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(54) Title: OXAZOLE DERIVATIVES, THEIR PRODUCTION AND USE

(57) Abstract

The present invention relates to oxazole derivatives having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, their production and use. The oxazole derivatives of the present invention have excellent IL-6 inhibitory activity and NO production inhibitory activity of NOS inducible cells, and can be used as a prophylactic or a therapeutic drug for IL-6-associated diseases or NO-associated diseases.

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DESCRIPTION

OXAZOLE DERIVATIVES, THEIR PRODUCTION AND USE

[Technical Field]

The present invention relates to oxazole derivatives having inhibitory activity of interleukin-6 (IL-6) activity and that of nitrogen monoxide (NO) production of NOS inducible cells, which are of value as medicines for prophylaxis and therapy of heart diseases, autoimmune diseases, inflammatory diseases and diseases accompanied by granuloma, among other morbidities, to processes for its production, and to pharmaceutical compositions comprising said derivatives.

[Background Art]

Interleukin-6 (hereinafter referred to briefly as IL-6) is a glycoprotein with a molecular mass of 26kDa as initially cloned as B-cell stimulatory factor. This cytokine is produced in T- and B-lymphocytes, monocytes, fibroblasts, keratinocytes, vascular endothelial cells, renal mesangial cells, brain astrocytes and osteoblasts. Its multifunctional physiological activity encompasses the immune system, hematopoietic system, cerebroneural system, inflammatory system, endocrine system, etc. Thus, IL-6 specifically functions as 1) antibody production inducing factor, 2) hybridoma/plasmacytoma/myeloma growth factor, 3) T-lymphocyte growth factor/killer T-cell differentiation factor, 4) hematopoietic stem cell growth factor, 5) megakaryocyte maturation factor/platelet proliferation factor, 6) nerve cell stimulating factor, 7) hepatocyte stimulatory factor, 8) osteoclast activating factor, 9) renal mesangial cell growth factor, and 10) ACTH production inducing factor, etc. [The Cytokine Handbook, 2nd Ed., Academic Press, USA., pp.145-168 (1994)].

Recently IL-6 has been to be involved in the various diseases, namely cardiac diseases such as myocardiopathy, cardiac hypertrophy, myocardial infarction, angina pectoris, etc., various autoimmune diseases such as chronic rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, rheumatic fever, polymyositis, periarteritis nodosa, Sjögren's syndrome, Behcet's disease, Castleman's disease, autoimmune hemolytic anemia, etc., inflammatory diseases such as mesangial proliferative nephritis, IgA nephritis, lupus nephritis, osteoporosis, bronchial asthma, atopic dermatitis, psoriasis, pleurisy, ulcerative colitis, atherosclerosis, active chronic hepatitis, alcoholic cirrhosis, gout, various types of encephalitis, etc., and diseases accompanied by granuloma such as multiple myeloma, atrial myxoma, renal carcinoma, pulmonary adenocarcinoma, malignant mesothelioma, ovarian cancer, cancerous cachexia, and so on.

In fact, in patients with chronic rheumatoid arthritis, high level of IL-6 is detected in the synovial fluid, with the definite expression of IL-6 mRNA in the synovial membrane. And administration of anti-IL-6 antibody to such patients resulted in symptomatic improvements [The Journal of Rheumatology, 20, 259-261 (1993)]. In regard to glomerulonephritis, while mesangial proliferative nephritis accompanied by advanced proteinurea was found in IL-6 transgenic mice, administration of anti-IL-6 antibody resulted in remission of the symptoms [Japanese Journal of Clinics, 50, 2840-2841 (1992)]. Moreover, in human proliferative glomerulonephritis inclusive of IgA nephritis, the urinary IL-6 level is elevated in proportion to the degree of progression of tissue damage and, therefore, IL-6 is utilized as a clinical marker. In postmenopausal osteoporosis with decreased

estrogen production, IL-6 acts as osteoclast activating factor and exhibits potent bone resorption activity. In ovariectomized mice, osteoclasts proliferate but this proliferation is inhibited by anti-IL-6 antibody [Science, 257, 88-91 (1992)]. In IL-6 gene-deficient mice, no bone destruction took place even after ovariectomy. These reports indicate the involvement of IL-6 in the above-mentioned diseases and suggest that symptomatic improvements can be obtained by inhibiting the physiological activity of IL-6.

For inhibition of the physiological activity of IL-6, both inhibition of IL-6 production and inhibition of IL-6 activity can be contemplated. As regards the former approach, 4H-1-benzopyran-4-one derivatives have been reported to be inhibitors of IL-6 production [Japanese laid-open patent application 49778/1990]. In contrast, the latter approach remains to be explored as yet (and is by nature a very singular approach), and most of the reports so far made in this area are concerned with macromolecular substances such as antibodies and peptides which are not suitable for administration [The European Journal of Immunology, 18, 951-956 (1988)].

Nitrogen monoxide (NO) is considered to play multi-faceted roles in the mammalian body, for example as a vasodilating factor in the vascular system [Pharmacol. Rev. 43, 109-142 (1991)], as a factor having tumoricidal and germicidal activity in the leukocytic system [Curr. Opin. Immunol., 3, 65-70 (1991)], and as a neurotransmitter in the nervous system, among others [Neuron, 8, 3-11 (1992)].

NO is produced from L-arginine by NO synthase (NOS). Today, three isozymes, namely neural NOS, vascular endothelial NOS and inducible NOS (iNOS), have been identified [Cell, 70, 705-707 (1992)]. Based on the mode of production, the former two isozymes are

also known as constitutive NOS (cNOS) in antithesis to the third one iNOS. cNOS exists in the vascular endothelial cells and nerve cells. cNOS is calcium/calmodulin-dependent and activated by various receptor stimuli to produce a small amount of NO, thus carrying out the physiological modulations mentioned above. On the other hand, iNOS is induced by various cytokines and bacterial lipopolysaccharides (LPS) in the macrophages and neutrophils and it has been pointed out that because it produces a large amount of NO persistently, iNOS not only shows the above-mentioned physiological activities but, when produced locally, injures the cells and tissues [Immunol. Today, 13, 157-160 (1992)]. As the cells and tissues in which iNOS is expressed, not only the above-mentioned cells but also hepatocytes, Kupffer cells, gliacytes, vascular smooth muscle cells, vascular endothelial cells, heart muscle lining, myocardial cells, mesangial cells, chondrocytes, sinovial cells, pancreatic β cells and osteoclasts are known [FASEB J., 6, 3051-3064 (1992), Arch Surg., 128, 396-401 (1993), J. Biol. Chem., 44, 27580-27588 (1994), J. Cell. Biochem., 57, 399-408 (1995)]. It is, therefore, conceivable that NO produced in these cells and tissues is involved in various diseases. Therefore, any substance that inhibits production and release of NO from cells in which iNOS has been induced is expected to be of value as a drug for prevention and therapy of various NO-associated diseases such as, for example, atherosclerosis, myocarditis, myocardiopathy, ischemic brain disorder, Alzheimer's disease, multiple sclerosis, septicemia, chronic rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerulonephritis, osteoporosis, pneumonia, hepatitis, graft rejection and pain.

From the above points of view, L-arginine analogues [Pharmacol. Rev., 43, 109-142 (1991)], aminoguanidine [Br. J. Pharmacol., 110, 963-968 (1993), and S-ethylisothiourea [J. Biol. Chem., 43, 26669-26676 (1994)], among others, have been reported for use as inhibitors of iNOS. However, these compounds are either not sufficiently active or inhibit not only iNOS but also cNOS which is in charge of physiological functions.

Various drugs have heretofore been used in the treatment of heart diseases, autoimmune diseases, inflammatory diseases, and diseases accompanied by granuloma but none of them are fully satisfactory in efficacy or in safety. Therefore, development of drugs improved in these aspects has been awaited for the prevention and treatment of heart diseases, autoimmune diseases, inflammatory diseases, and diseases accompanied by granuloma.

Some oxazole derivatives were described in Chem. Mater., 1994, 6(7) 1023-1032, Chem. Abs. 107:96787 and EP-A 879539. However, inhibition of IL-6 activity and NO production of the oxazole derivatives of this invention has not been disclosed anywhere.

[Disclosure of Invention]

After intensive research for solving the above-mentioned problems, the inventors of the present invention discovered surprisingly that oxazole derivatives having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring have excellent IL-6 inhibitory activity and NO production inhibitory activity of NOS inducible cells and are effective in the prevention and therapy of heart diseases, autoimmune diseases, inflammatory diseases, and diseases accompanied by granuloma. The

inventors thenceforth did further research and have completed the present invention.

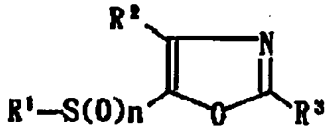
The present invention accordingly provides:

1. An oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, provided that when the substituent at the 4-position is hydrogen, (1) the compound which has 4-methoxyphenyl or 4-methoxyphenylethinyl at the 2-position and nonafluorobutylsulfonyl at the 5-position, (2) the compound which has phenyl at the 2-position and (2-phenyl-5-thiazolyl)sulfonyl at the 5-position, and (3) the compound which has 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl at the 2-position and 4-methylphenylsulfonyl at the 5-position are excluded;

2. The oxazole derivative as described in 1, which has a halogen atom or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom as a substituent at the 2-position of the oxazole ring;

3. The oxazole derivative as described in 1, which has a halogen atom or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom as a substituent at the 4-position of the oxazole ring;

4. The oxazole derivative as described in 1, which is a compound of the formula:



(I)

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n

represents 1 or 2; R^2 represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted, or carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -S(O)m-R; where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2;

5. The oxazole derivative as described in 4, wherein R^1 represents a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, or amino which may be substituted;
R^2 represents hydrogen, cyano, an organic carboxylic acid-derived acyl group, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, amino which may be substituted, or carboxyl which may be esterified;
R^3 represents hydrogen, halogen, a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, a C_{1-19} hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula

-S(O)m-R'; where R' represents a C_{1-19} hydrocarbon group which may be substituted or a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted; m represents 0, 1, or 2;

6. The oxazole derivative as described in 4, wherein R^1 represents

(1) C_{1-19} alkyl which may be substituted with (i) a 5- or 6-membered sulfur-containing heterocyclic group, (ii) a 5- or 6-membered oxygen- and nitrogen-containing heterocyclic group which may be substituted with C_{1-12} alkyl or cyano, (iii) carboxyl, (iv) C_{6-14} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be mono- or di-substituted with C_{1-12} alkyl, or (vii) C_{1-12} alkoxy-carbonyl,

(2) C_{2-12} alkenyl which may be substituted with mono- or di-C_{1-12} alkylamino,

(3) C_{2-12} alkinyl,

(4) C_{3-10} cycloalkyl,

(5) C_{6-14} aryl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which may be substituted with C_{1-12} alkyl or C_{3-10} cycloalkyl, (b) C_{6-14} arylsulfonyl which may be substituted with halogen, or (c) C_{1-12} alkylsulfonyl, (iv) C_{1-12} alkyl which may be substituted with halogen, (v) nitro or (vi) hydroxyl,

(6) C_{7-19} aralkyl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl or (b) C_{1-12} alkylsulfonyl, or (iv) nitro,

(7) a 5- or 6-membered nitrogen- or oxgen-containing heterocyclic group,

(8) amino which may be substituted with (i) C_{1-12} alkyl

which may be substituted with (a) C_{1-12} alkoxy-carbonyl, (b) mono- or di-C_{1-12} alkylamino or (c) a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{7-19} aralkyl which may be substituted with halogen or C_{1-12} alkoxy, (iii) C_{4-12} bridged-ring hydrocarbon group, (iv) C_{6-14} aryl or (v) C_{3-10} cycloalkyl or
(9) thienopyrimidylhydrazino which may be substituted with C_{1-12} alkyl;

7. The oxazole derivative as described in 4, wherein R^1 represents
(1) C_{1-12} alkyl which may be substituted with (i) thienyl, (ii) oxazolyl which may be substituted with C_{1-6} alkyl or cyano, (iii) carboxy, (iv) C_{6-12} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be mono- or di-substituted with C_{1-6} alkyl, or (vii) C_{1-6} alkoxy-carbonyl,
(2) C_{2-6} alkenyl which may be substituted with mono- or di-C_{1-6} alkylamino,
(3) C_{2-6} alkinyl,
(4) C_{3-8} cycloalkyl,
(5) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which is substituted with C_{1-6} alkyl or C_{3-8} cycloalkyl, (b) C_{6-12} arylsulfonyl which may substituted with halogen or (c) C_{1-6} alkylsulfonyl, (iv) C_{1-6} alkyl which may be substituted with halogen (v) nitro or (vi) hydroxy,
(6) C_{7-13} aralkyl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl or (b) C_{1-6} alkylsulfonyl, or (iv) nitro,
(7) a heterocyclic group selected from the group

consisting of pyrimidyl, piperidino, morpholino and 1-piperazinyl,
(8) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with (a) C_{1-6} alkoxy-carbonyl, (b) mono- or di-C_{1-6} alkylamino or (c) pyridyl, (ii) C_{6-12} aryl, (iii) C_{7-13} aralkyl which may be substituted with halogen or C_{1-6} alkoxy, (iv) adamantyl or (v) C_{3-8} cycloalkyl, or
(9) thienopyrimidylhydrazino which may be substituted with C_{1-6} alkyl;

8. The oxazole derivative as described in 4, wherein R^2 represents
(1) cyano,
(2) C_{1-12} alkanoyl,
(3) carbamoyl which may be substituted with (i) C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{1-12} alkoxy or (iii) C_{7-19} aralkyl,
(4) a 5- or 6-membered saturated nitrogen-containing heterocyclic-carbonyl, which may be substituted with C_{6-14} aryl,
(5) thiocarbamoyl which may be substituted with (i) C_{1-12} alkyl or (ii) C_{7-19} aralkyl,
(6) a 5- or 6-membered saturated nitrogen-containing heterocyclic-thiocarbonyl,
(7) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of (i) hydroxyl which may be acylated with C_{6-14} arylcarbonyl, (ii) halogen, (iii) carboxyl, (iv) cyano, (v) amino which may be substituted with C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group or C_{7-19} aralkyl, (vi) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms, which may be substituted with C_{6-14}

aryl, (vii) phthalimido, (viii) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl, and (ix) C_{6-14} aryloxy which may be substituted with halogen,
(8) C_{7-19} aralkyl which may be substituted with halogen or hydroxyl,
(9) a 5- or 6-membered nitrogen and sulfur-containing heterocyclic group, which may be substituted with (i) C_{1-12} alkoxy-carbonyl or (ii) C_{6-14} aryl,
(10) amino which may be substituted with C_{1-12} alkoxy-carbonyl,
(11) carboxyl, or
(12) C_{1-12} alkoxy-carbonyl;

9. The oxazole derivative as described in 4, wherein R^2 represents
(1) cyano,
(2) C_{1-6} alkanoyl,
(3) carbamoyl which may be substituted with (i) C_{1-6} alkyl which may be substituted with pyridyl, (ii) C_{7-13} aralkyl or (iii) C_{1-6} alkanoyl,
(4) piperidinocarbonyl,
(5) 1-piperazinylcarbonyl which may be substituted with C_{6-12} aryl,
(6) thiocarbamoyl which may be substituted with (i) C_{1-6} alkyl or (ii) C_{7-13} aralkyl,
(7) piperidinothiocarbonyl,
(8) C_{1-6} alkyl which may be substituted with (i) hydroxy which may be acylated with C_{6-12} arylcarbonyl, (ii) halogen, (iii) carboxyl, (iv) cyano, (v) amino which may substituted with (a) C_{1-6} alkyl which may be substituted with pyridyl or (b) C_{7-13} aralkyl, (vi) 1-piperazinyl which may be substituted with C_{6-12} aryl, (vii) phthalimido, (viii) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, or (ix) C_{6-12} aryloxy which may be substituted with halogen,

(9) C_{7-13} aralkyl which may be substituted with halogen or hydroxyl,
(10) thiazolyl which may be substituted with C_{1-6} alkoxy-carbonyl or (b) C_{6-12} aryl,
(11) amino which may be substituted with C_{1-6} alkoxy-carbonyl,
(12) carboxyl, or
(13) C_{1-6} alkoxy-carbonyl;

10. The oxazole derivative as described in 4, wherein R^3 represents
(1) hydrogen,
(2) halogen,
(3) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of (i) amino which may be substituted with C_{7-19} aralkyl or C_{1-12} alkyl, (ii) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms which may be substituted with C_{6-14} aryl, (iii) phthalimido, (iv) C_{6-14} arylsulfonyl which may substituted with C_{1-12} alkyl, (v) hydroxyl which may be substituted with C_{1-12} alkanoyl, (vi) a 5- or 6-membered saturated nitrogen- and/or oxygen-containing heterocyclic group, (vii) halogen, (viii) C_{1-12} alkoxy-carbonyl, and (ix) a 5- to 6-membered unsaturated nitrogen- and/or oxgen-containing heterocyclic group, which may be substituted with C_{1-6} alkyl or cyano,
(4) C_{2-12} alkenyl which may be substituted with C_{6-14} aryl,
(5) C_{6-14} aryl which may be substituted with C_{1-12} alkoxy,
(6) C_{7-19} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) C_{1-12} alkoxy, or (iv) halogen,
(7) C_{3-10} cycloalkyl,
(8) C_{3-10} cycloalkyl-C_{1-12} alkyl,
(9) a C_{4-12} bridged-ring hydrocarbon group,

(10) a 5- to 6-membered unsaturated nitrogen- and/or oxygen-containing heterocyclic group,
(11) C_{1-12} alkoxy,
(12) amino which may be substituted with (i) C_{1-12} alkyl which may substituted with C_{1-12} alkoxy-carbonyl or (b) a 5- or 6-membered nitrogen-containing heterocyclic group or (ii) C_{7-19} aralkyl, or
(13) C_{1-12} alkoxy-carbonyl;

11. The oxazole derivative as described in 4, wherein R^3 represents
(1) hydrogen,
(2) halogen,
(3) C_{1-6} alkyl which may be substituted with (i) amino which may be substituted with C_{7-13} aralkyl or C_{1-6} alkyl, (ii) 1-piperazinyl which may be substituted with C_{6-12} aryl, (iii) phthalimide, (iv) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, (v) hydroxyl which may be substituted with C_{1-6} alkanoyl, (vi) morpholino, (vii) piperidino, (viii) halogen, (ix) C_{1-6} alkoxy-carbonyl, and (x) oxazolyl which may be substituted with C_{1-6} alkyl or cyano,
(4) C_{2-6} alkenyl which may be substituted with C_{6-12} aryl,
(5) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy,
(6) C_{7-13} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) Cl-6 alkoxy, or (iv) halogen,
(7) C_{3-8} cycloalkyl,
(8) C_{3-8} cycloalkyl-C_{1-6} alkyl,
(9) adamantyl,
(10) oxadiazolyl,
(11) C_{1-6} alkoxy,
(12) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with C_{1-6} alkoxy-carbonyl or

pyridyl, or (ii) C_{7-13} aralkyl, or
(13) C_{1-6} alkoxy-carbonyl;

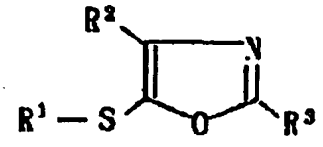
12. The oxazole derivative as described in 4, wherein R^1 represents (1) C_{1-6} alkyl which may be substituted with (i) 2-thienyl or (ii) carboxyl, (2) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy or (iii) C_{1-6} alkylcarbamoylamino, (3) C_{7-13} aralkyl which may be substituted with nitro, (4) amino which may be substituted with (i) C_{1-6} alkyl, (ii) C_{6-12} aryl or (iii) C_{3-8} cycloalkyl, or (5) morpholino;

13. The oxazole derivative as described in 4, wherein R^2 represents cyano, thiocarbamoyl, carbamoyl, or C_{1-6} alkyl which may be substituted with halogen;

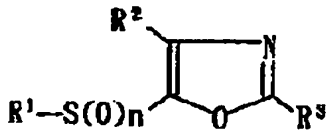
14. The oxazole derivative as described in 4, wherein R^3 represents (1) hydrogen, (2) C_{1-6} alkyl which may be substituted with amino which may have C_{1-6} alkyl or C_{7-15} aralkyl substituent, (3) C_{3-6} cycloalkyl, (4) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy or (5) C_{7-13} aralkyl which may be substituted with (i) halogen or (ii) C_{1-6} alkoxy;

15. The oxazole derivative as described in 4, wherein n is 2;

16. A process for producing the oxazole derivative as described in 4, which comprises
(1) oxidizing a compound of the formula:

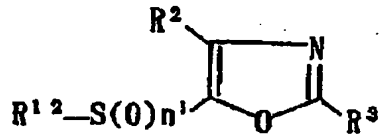


wherein R^1, R^2, and R^3 are as defined in 4 to obtain an oxazole derivative of the formula:



wherein R^1, R^2, and R^3 are as defined above, and n is as defined in 4,

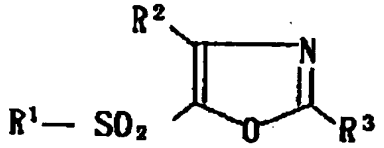
(2) reacting a compound of the formula:



wherein R^2 and R^3 are as defined above; R^{12} represents lower alkyl or phenyl; n^1 is 0, 1, or 2 with a compound of the formula:

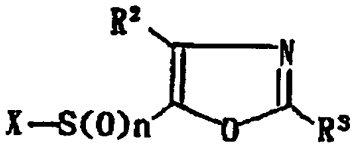
$$R^1\text{-}SO_2M$$

wherein R^1 is as defined above; M represents an alkali metal to obtain an oxazole derivative of the formula:



wherein R^1, R^2, and R^3 are as defined above, or

(3) reacting a compound of the formula:

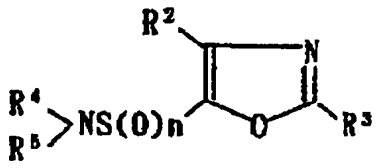


wherein R^2, R^3, and n are as defined above; X represents a leaving group with a compound of the

formula:

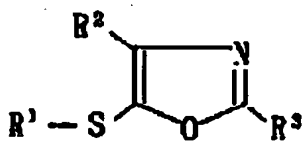
$$HNR^4R^5$$

wherein R^4 and R^5 independently represent hydrogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted; R^4 and R^5 may be combined with the adjacent nitrogen atom to form a heterocyclic group to obtain an oxazole derivative of the formula:



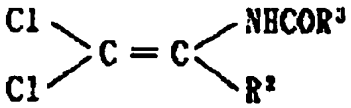
wherein R^2, R^3, n, R^4, and R^5 are as defined above;

17. A process for producing a compound of the formula:



wherein R^1, R^2, and R^3 are as defined in 4 which comprises

(1) reacting a compound of the formula:



wherein R^2 and R^3 are as defined above with a compound of the formula:

$$M_2S$$

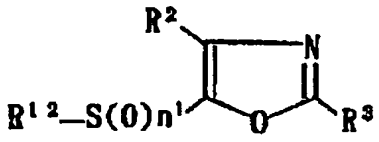
wherein M represents an alkali metal and a compound of the formula:

$$R^1X$$

wherein R^1 is as defined above; X represents a leaving

group, or

(2) reacting a compound of the formula:

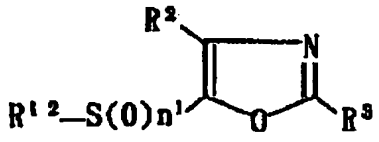


wherein R^2 and R^3 are as defined above; R^{12} represents lower alkyl or phenyl; n^1 is 0, 1, or 2 with a compound of the formula:

$$R^1\text{-}SH$$

wherein R^1 are as defined above, or

(3) reacting a compound of the formula:



wherein R^2, R^3, R^{12} and n^1 are as defined above with a compound of the formula:

$$M_2S$$

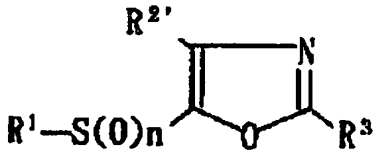
wherein M is as defined above and a compound of the formula:

$$R^1X$$

wherein R^1 and X are as defined above;

18. A pharmaceutical composition comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring;

19. The pharmaceutical composition as described in 18, wherein the oxazole derivative is a compound of the formula:



(I')

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n represents 1 or 2; $R^{2'}$ represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted, or carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -S(O)m-R, where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2;

20. The pharmaceutical composition as described in 18 or 19, which is a prophylactic or therapeutic pharmaceutical for cardiac diseases, autoimmune diseases, inflammatory diseases, or diseases accompanied by granuloma;

21. The pharmaceutical composition as described in 18 or 19, which is a prophylactic or therapeutic pharmaceutical for myocardiopathy, cardiac hypertrophy, myocardial infarction, angina pectoris, chronic rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, rheumatic fever, polymyositis, periarteritis nodosa, Sjögren's syndrome, Behcet's

disease, Castleman's disease, autoimmune hemolytic anemia, mesangial proliferative nephritis, IgA nephritis, lupus nephritis, osteoporosis, amyloidosis, bronchial asthma, atopic dermatitis, psoriasis, pleurisy, ulcerative colitis, atherosclerosis, active chronic hepatitis, alcoholic cirrhosis, gout, encephalitis, multiple myeoloma, atrial myxoma, renal carcinoma, pulmonary adenocarcinoma, malignant mesothelioma, ovarian cancer or cancerous cachexia;

22. A composition for inhibition of interleukin-6 activity comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring;

23. The pharmaceutical composition as described in 18 or 19, which is a prophylactic or therapeutic pharmaceutical for atherosclerosis, myocarditis, myocardiopathy, ischemic brain disorder, Alzheimer's disease, multiple sclerosis, septicemia, chronic rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerulonephritis, osteoporosis, pneumonia, hepatitis, graft rejection or pain;

24. A composition for inhibition of nitrogen monoxide production comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring;

25. Use of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, for the manufacture of a medicament for inhibiting interleukin-6 activity;

26. Use of an oxazole derivative having a group bonded

through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, for the manufacture of a medicament for inhibiting nitrogen monoxide production;

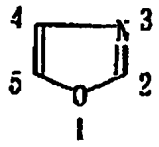
27. A method for inhibiting interleukin-6 activity in human or mammal, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal;

28. A method for preventing or treating interleukin-6-associated diseases, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal;

29. A method for inhibiting a nitrogen monoxide production in human or mammal, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal; or

30. A method for preventing or treating nitrogen monoxide-associated diseases, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal.

The oxazole ring forming the skeletal structure of the compound of the present invention can be expressed by the following formula:



Compound A according to the present invention is an oxazole derivative having a group bonded through a sulfinyl (-SO-) or sulfonyl ($-SO_2-$) moiety at the 5-position of the oxazole ring provided that when the substituent at the 4-position is hydrogen, (1) the compound which has 4-methoxyphenyl or 4-methoxyphenylethinyl at the 2-position and nonafluorobutylsulfonyl at the 5-position, (2) the compound which has phenyl at the 2-position and (2-phenyl-5-thiazolyl)sulfonyl at the 5-position, and (3) the compound which has 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl at the 2-position and 4-methylphenylsulfonyl at the 5-position are excluded.

The 2-position of the oxazole ring may be unsubstituted but may be substituted, for example by a halogen atom or a suitable group which is bonded through a carbon, nitrogen, oxygen, or sulfur atom.

The 4-position of the oxazole ring may be unsubstituted but may be substituted, for example by a halogen atom or a suitable group which is bonded through a carbon, nitrogen, oxygen, or sulfur atom.

The substituent group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring may be any group which is bonded through a sulfinyl group or a sulfonyl group. Such a group can be typically expressed by the formula:

$$R^1\text{-}S(O)_n\text{-}$$

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n is 1

or 2.

The halogen atom which can be used includes fluorine, chlorine, bromine, and iodine.

The substituent group bonded through a carbon atom at the 2- or 4-position of the oxazole ring may for example be a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted (this heterocyclic group is linked via a ring carbon atom at the 2- or 4-position of the oxazole ring), -CN-, -$COOR^a$, -$CO-R^a$, -$CO-NR^aR^b$, -$CS-NR^aR^b$, -$CO-SR^a$, -$CS-SR^a$, -$CO-NR^a-CO-R^b$, and -$C(=NH)-NR^aR^b$.

The substituent group bonded through a nitrogen atom at the 2- or 4-position may for example be -NR^aR^b, -NR^a-CO-R^b, -NR^a-CS-R^b, -$NR^c-CO-NR^aR^b$, -$NR^c-CS-NR^aR^b$, -$NR^a-CO-OR^b$, -$NR^a-CS-OR^b$, -$NR^a-CO-SR^b$, -$NR^a-CS-SR^b$, -$NR^c-C(=NH)-NR^aR^b$, -$NR^a-SO_2R^b$ and -$NR^c-NR^aR^b$.

The group bonded through an oxygen atom at the 2- or 4-position may for example be OR^a, -$O-CO-R^a$, -$O-CS-R^a$, -$O-CO-OR^a$, -$O-CO-NR^aR^b$, and -$O-C(=NH)-NR^a$.

The substituent group bonded through a sulfur atom at the 2- or 4-position may for example be -SR^a, -$SO-R^a$, -SO_2-R^a, -$SO_2NR^aR^b$, -$S-CO-R^a$, -$S-CS-R^a$, -$S-CO-NR^aR^b$, -$S-CS-NR^aR^b$, -$S-C(=NH)NR^aR^b$, and -SCN.

R^a, R^b, and R^c, mentioned above, may be independently represents hydrogen, a hydrocarbon group which may be substituted, or a heterocyclic group which may be substituted. Where -NR^aR^b exists as part of the substituent group, R^a and R^b may be combine with the adjacent nitrogen atom to form a heterocyclic ring.

The hydrocarbon group for "the group bonded through a carbon atom" for the 2- or 4-substituent and the hydrocarbon group for R^1, R^a, R^b, or R^c includes alkyl, alkenyl, alkinyl, cycloalkyl, aryl, aralkyl and bridged-ring hydrocarbon groups. Particularly preferred are C_{1-24} hydrocarbon groups.

The alkyl group is preferably a straight-chain or branched alkyl group of 1-24 carbon atoms (C_{1-24} alkyl). Thus, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-octadecyl, n-eicosyl, n-docosyl, n-tetracosyl, etc. can be mentioned. The preferred alkyl group is a straight-chain or branched alkyl group of 1-19 carbon atoms (C_{1-19} alkyl) and the more preferred is a straight-chain or branched alkyl group of 1-12 carbon atoms (C_{1-12} alkyl). Particularly preferred is a straight-chain or branched alkyl group of 1-6 carbon atoms (C_{1-6} alkyl).

The alkenyl group is preferably a straight-chain or branched alkenyl group of 2-24 carbon atoms (C_{2-24} alkenyl), thus including vinyl, propeny(1-, 2-), butenyl(1-, 2-, 3-), pentenyl, octenyl, butadienyl(1, 3-), etc. The preferred alkenyl is a straight-chain or branched alkenyl group of 2-19 carbon atoms (C_{2-19} alkenyl) and the more preferred is a straight chain or branched alkenyl group of 2-12 carbon atoms (C_{2-12} alkenyl). Particularly preferred is a straight-chain or branched alkenyl group of 2-6 carbon atoms (C_{2-6} alkenyl).

The alkinyl group is preferably a straight-chain or branched alkinyl group of 2-24 carbon atoms (C_{2-24} alkinyl), thus including ethinyl, propinyl(1-, 2-), butinyl(1-, 2-, 3-), pentinyl, octinyl, decinyl, etc. The preferred alkinyl is a straight-chain or branched alkinyl group of 2-19 carbon atoms (C_{2-19} alkinyl) and the more preferred is a straight chain or branched alkinyl group of 2-12 carbon atoms (C_{2-12} alkinyl). Particularly preferred is a straight-chain or branched

alkinyl group of 2-6 carbon atoms (C_{2-6} alkinyl).

The cycloalkyl group is preferably a group of 3-10 carbon atoms (C_{3-10} cycloalkyl), thus including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The more preferred is a cycloalkyl group of 3-8 carbon atoms (C_{3-8} cycloalkyl). Particularly preferred is a cycloalkyl group of 3-6 carbon atoms (C_{3-6} cycloalkyl).

The aryl group may for example be a monocyclic group or a fused polycyclic group and is preferably a group containing 6-18 carbon atoms (C_{6-18} aryl). Thus, for example, phenyl, biphenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, etc. can be mentioned. The preferred aryl group is a group of 6-14 carbon atoms (C_{6-14} aryl), such as phenyl and naphthyl. Particularly preferred is an aryl group of 6-12 carbon atoms (C_{6-12} aryl).

The aralkyl group may for example be an alkyl group substituted by a mono- to tri-cyclic aromatic hydrocarbon group and is preferably an alkyl group of 1-24 carbon atoms which has been substituted by an aryl group of 6-18 carbon atoms (C_{6-18} aryl-C_{1-24} alkyl). Among such aralkyl groups are benzyl, biphenylylmethyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl, 2-naphthylmethyl, etc. Among them, C_{7-19} aralkyl groups are preferred and C_{7-13} aralkyl groups are particularly preferred.

The bridged-ring hydrocarbon group is preferably a group of 4-19 carbon atoms (C_{4-19} bridged-ring hydrocarbon group), thus including 1-adamantyl, 2-adamantyl, 2-norbornanyl and 5-norbornen-2-yl. The more preferred is a bridged-ring hydrocarbon group of 4-12 carbon atoms (C_{4-12} bridged-ring hydrocarbon group).

The heterocyclic group mentioned for the "group

bonded through a carbon atom" for the 2- or 4-substituent and the heterocyclic group for R^1, R^a, R^b and R^c may for example be a 5- to 8-membered heterocyclic group containing 1-4 hetero-atoms selected from oxygen, sulfur and nitrogen in addition to carbon as ring members, or a condensed heterocyclic group thereof (e.g. a condensed heterocyclic group with a 6- to 8-membered carbocyclic or a heterocyclic group).

Specifically, the heterocyclic group includes 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido-2-, 3- or 4-pyridyl, N-oxido-2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo[1,5-b]pyridazinyl, triazolo[1,5-b]pyridazinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, piperidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, morpholinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, thienopyrimidinyl etc.

Preferred among those heterocyclic groups are 5- or 6-membered heterocyclic groups containing at least one nitrogen atom. In particular, pyrimidinyl, thiazolyl and oxadiazolyl are preferred.

The substituent group for groups which may be

present on the above-mentioned "hydrocarbon group" or "heterocyclic group" includes but is not limited to C_{1-12} alkyl groups (preferably C_{1-6} alkyl, more preferably C_{1-4} alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl), C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl), halogen (e.g. fluorine, chlorine, bromine, and iodine), cyano, hydroxyl which may be acylated (preferably hydroxyl which may be acylated with C_{1-12} alkanoyl, C_{6-14} arylcarbomyl or C_{7-13} aralkanoyl such as carboxyl, C_{1-12} alkanoyloxy (e.g. acetyloxy), C_{6-14} arylcarbonyloxy (e.g. benzoyloxy) and C_{7-13} aralkanoyloxy (e.g. benzylcarbonyloxy)), C_{1-12} alkoxy (preferably C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, and butoxy), C_{6-14} aryloxy (e.g. phenyloxy, naphthyloxy, etc.), carboxyl, C_{1-12} alkoxy-carbonyl (preferably C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl), nitro, carbamoyl which may be substituted with C_{1-12} alkyl (e.g. butylcarbamoyl), C_{1-12} alkanoyl (preferably C_{1-6} alkanoyl such as formyl, acetyl, propionyl, and butyryl), C_{6-14} aryl (e.g. phenyl, naphthyl, etc.), C_{6-14} arylcarbonyl (e.g. benzoyl, naphthoyl, etc.), C_{7-13} aralkyl-carbonyl (e.g. benzylcarbonyl) heterocyclic groups [e.g. 3- to 8-membered heterocyclic groups containing 1-4 hetero-atoms selected from nitrogen, oxygen, and sulfur in addition to carbon as ring members and the condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic or heterocyclic group, such as furyl(2-, 3-), thienyl(2-, 3-), pyridyl(2-, 3-, 4-), thiazolyl, imidazolyl, benzothiazolyl, benzimidazolyl, oxazolyl (2-, 4, 5-) etc.], a group of the formula $-NR^dR^e$ (where R^d and R^e independently represents hydrogen, a hydro-carbon group which may be substituted, a heterocyclic

group which may be substituted, or $-SO_2R^f$ where R^f represents a hydrocarbon group which may be substituted; R^d and R^e may be combined with the adjacent nitrogen atom to form a heterocyclic ring, C_{1-12} alkylthio, C_{1-12} alkylsulfinyl, C_{1-12} alkylsulfonyl, C_{6-14} arylthio, C_{6-14} arylsulfinyl, C_{6-14} arylsulfonyl, etc.

Among the above-mentioned substituent groups, said C_{1-12} alkyl, C_{3-8} cycloalkyl, and the alkyl moiety of said C_{1-12} alkylthio, C_{1-12} alkylsulfinyl or C_{1-12} alkylsulfonyl may be further substituted with, for example, C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, iodine), cyano, hydroxyl, C_{1-12} alkoxy (preferably C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, and butoxy), carboxyl, C_{1-12} alkoxy-carbonyl (preferably C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl), nitro, amino, carbamoyl, and C_{1-12} alkyl-carbonyl (preferably C_{1-6} alkyl-carbonyl such as formyl, acetyl, propionyl, and butyryl).

Among the above-mentioned substituent groups, said C_{6-14} aryl and the C_{6-14} aryl moiety of said C_{6-14} aryl-carbonyl, C_{6-12} arylthio, C_{6-12} arylsulfinyl, or C_{6-12} arylsulfonyl may be further substituted with, for example, C_{1-6} alkyl (preferably C_{1-4} alkyl such as methyl, ethyl, propyl, and butyl), C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, and iodine), cyano, hydroxyl, C_{1-6} alkoxy (preferably C_{1-4} alkoxy such as methoxy, ethoxy, propoxy, and butoxy), carboxyl, C_{1-6} alkoxy-carbonyl (preferably C_{1-4} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl), nitro, amino, carbamoyl, C_{1-6} alkanoyl (preferably C_{1-4} alkyl-carbonyl

such as formyl, acetyl, propionyl, and butyryl).

Among the above-mentioned substituent groups, said heterocyclic group may be further substituted by, for example, C_{1-6} alkyl (preferably C_{1-4} alkyl such as methyl, ethyl, propyl, and butyl), C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, and iodine), cyano, hydroxyl, C_{1-6} alkoxy (preferably C_{1-4} alkoxy such as methoxy, ethoxy, propoxy, and butoxy), carboxyl, C_{1-6} alkoxy-carbonyl (preferably C_{1-4} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl), nitro, amino, carbamoyl, C_{1-6} alkanoyl (preferably C_{1-4} alkyl-carbonyl such as formyl, acetyl, propionyl, and butyryl).

Among the above-mentioned substituent groups, the hydrocarbon group or heterocyclic group represented by R^d, R^e, or R^f in the group of the formula $-NR^dR^e$ or $-SO_2-R^f$ may be the same as the hydrocarbon group or heterocyclic group defined for R^1 hereinbefore.

Where R^d and R^e are combined with the adjacent nitrogen atom to form a heterocyclic ring, the ring (i.e. the nitrogen-containing ring) may be a 5- to 8-membered nitrogen-containing group optionally containing 1-4 atoms selected from carbon, nitrogen, oxygen, and sulfur in addition to said nitrogen atom as ring members, which nitrogen-containing ring may be further fused to a 6- to 8-membered carbocyclic or heterocyclic group. Where R^d and R^e are combined with the adjacent nitrogen atom to form a heterocyclic ring, the group of the formula $-NR^dR^e$ constitutes a cyclic amino group. As specific examples of the cyclic amino group, there can be mentioned 1-pyrrolidinyl, 1-imidazolyl, piperidino (1-piperidyl), 1-piperazinyl, 3-oxazolidinyl, hexamethylenimino, heptamethylenimino, morpholino (4-morpholinyl), 1-indolinyl, and

phthalimido among others. These cyclic amino groups may each be further substituted.

The substituents for the hydrocarbon group or the heterocyclic group, represented by R^d or R^e, or the cyclic amino group $-NR^dR^e$ may be, for example, C_{1-4} alkyl (e.g. methyl, ethyl, propyl, butyl, etc.), C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, iodine), cyano, hydroxyl, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, etc.), carboxyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), nitro, amino, di-C_{1-4} alkylamino, carbamoyl, C_{1-4} alkyl-carbonyl (e.g. formyl, acetyl, propionyl, and butyryl), C_{6-12} aryl (e.g. phenyl, naphthyl, etc.) and 2-pyridyl.

The above-mentioned C_{1-4} alkyl and of said C_{3-8} cycloalkyl may be further substituted with, for example, C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, iodine), cyano, hydroxyl, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy), carboxyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl), nitro, amino, carbamoyl, and C_{1-4} alkyl-carbonyl (e.g. formyl, acetyl, propionyl, butyryl). The C_{6-12} aryl group mentioned above may also be further substituted by, for example, C_{1-4} alkyl (e.g. methyl, ethyl, propyl, butyl), C_{3-8} cycloalkyl (preferably C_{3-6} cycloalkyl such as cyclopentyl and cyclohexyl), halogen (e.g. fluorine, chlorine, bromine, iodine), cyano, hydroxyl, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy), carboxyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl), nitro, amino, carbamoyl, and C_{1-4} alkyl-carbonyl (e.g. formyl, acetyl, propionyl, butyryl, etc.).

The ring formed by R^a and R^b combined with the adjacent nitrogen atom can be the same kind of ring as the ring formed by R^d and R^e combined with the adjacent nitrogen atom.

The amino which may be substituted for R^1 may for example be a group of the formula $-NR^4R^5$, $-NR^a-CO-R^b$, $-NR^a-CO-NR^4R^5$, $-NR^a-CS-NR^4R^5$, $-NR^a-NR^4R^5$, or $-NR^a-CO-OR^b$ (where R^a, R^b, R^4 and R^5 independently represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; R^4 and R^5 may be combined with the adjacent nitrogen atom to form a heterocyclic ring).

The hydrocarbon group which may be substituted or the heterocyclic group which may be substituted, for R^4 or R^5, may be the same kind of group as "the hydrocarbon group which may be substituted" or "the heterocyclic group which may be substituted" for R^a or R^b. The ring formed by R^4 and R^5 combined with the adjacent nitrogen atom may be the same kind of ring as formed by R^d and R^e combined with the adjacent nitrogen atom.

The "group bonded through a sulfinyl or sulfonyl moiety" at the 5-position of the oxazole ring in compound A according to the present invention is preferably a group of the formula $R^1-S(O)n-$.

Here R^1 may for example be a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted. Particularly preferred is a hydrocarbon group which may be substituted or amino which may be substituted.

As to the value of n, both 1 and 2 are satisfactory but 2 is preferred.

The preferred substituent at the 2-position of compound A according to the present invention includes hydrogen, halogen, a hydrocarbon group which may be

substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted (for example, $-OR^a$), amino which may be substituted (for example, $-NR^aR^b$), carboxyl which may be esterified (for example, $-COR^a$) etc.

The preferred substituent at the 4-position of compound A according to the present invention includes hydrogen, cyano, acyl ($-COR^a$), carbamoyl which may be substituted ($-CO-NR^6R^7$), thiocarbamoyl which may be substituted ($-CS-NR^6R^7$), a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted (for example, $-NR^a-COOR^b$), carboxyl which may be esterified (for example, $-COOR^a$), etc.

In particular, cyano, acyl ($-COR^a$), carbamoyl which may be substituted ($-CO-NR^6R^7$), thiocarbamoyl which may be substituted ($-CS-NR^6R^7$), a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, and carboxyl which may be esterified ($-COOR^a$) are preferred.

More specifically, the preferred substituent at the 5-position is a group of the formula $R^1-S(O)n-$, where R^1 is preferably one of the following groups (1)-(9).

(1) C_{1-19} alkyl which may be substituted with (i) a 5- or 6-membered sulfur-containing heterocyclic group, (ii) a 5- or 6-membered oxygen- and nitrogen-containing heterocyclic group which may be substituted with C_{1-12} alkyl or cyano, (iii) carboxyl, (iv) C_{6-14} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be substituted with mono- or di-C_{1-12} alkyl, or (vii) C_{1-12} alkoxy-carbonyl.

(2) C_{2-12} alkenyl which may be substituted with mono- or di-C_{1-12} alkylamino.

(3) C_{2-12} alkinyl.

(4) C_{3-10} cycloalkyl.

(5) C_{6-14} aryl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which may be substituted with C_{1-12} alkyl or C_{3-10} cycloalkyl, (b) C_{6-14} arylsulfonyl which may be substituted with halogen, or (c) C_{1-12} alkylsulfonyl, (iv) C_{1-12} alkyl which may be substituted with halogen, (v) nitro or (vi) hydroxyl.

(6) C_{7-19} aralkyl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl or (b) C_{1-12} alkylsulfonyl, or (iv) nitro.

(7) a 5- or 6-membered nitrogen- or oxgen-containing heterocyclic group.

(8) amino which may be substituted with (i) C_{1-12} alkyl which may be substituted with (a) C_{1-12} alkoxy-carbonyl, (b) mono- or di-C_{1-12} alkylamino or (c) a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{7-19} aralkyl which may be substituted with halogen or C_{1-12} alkoxy, (iii) C_{4-12} bridged-ring hydrocarbon group, (iv) C_{6-14} aryl or (v) C_{3-10} cycloalkyl.

(9) thienopyrimidylhydrazino which may be substituted with C_{1-12} alkyl.

R^1 is more preferably one of the group of the following groups (1) - (12).

(1) C_{1-12} alkyl which may be substituted with (i) thienyl, (ii) oxazolyl which may be substituted with C_{1-6} alkyl or cyano, (iii) carboxyl, (iv) C_{6-12} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be substituted with mono- or di-C_{1-6} alkyl, or (vii) C_{1-6} alkoxy-carbonyl.

(2) C_{2-6} alkenyl which may be substituted with mono- or di-C_{1-6} alkylamino.

(3) C_{2-6} alkinyl.

(4) C_{3-8} cycloalkyl.

(5) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which is substituted with C_{1-6} alkyl or C_{3-8} cycloalkyl, (b) C_{6-12} arylsulfonyl which may substituted with halogen or (c) C_{1-6} alkylsulfonyl, (iv) C_{1-6} alkyl which may be substituted with halogen (v) nitro or (vi) hydroxy.

(6) C_{7-13} aralkyl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl or (b) C_{1-6} alkylsulfonyl, or (iv) nitro.

(7) a heterocyclic group selected from the group consisting of pyrimidyl, piperidino, morpholino and 1-piperazinyl.

(8) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with (a) C_{1-6} alkoxy-carbonyl, (b) mono- or di-C_{1-6} alkylamino or (c) pyridyl, (ii) C_{6-12} aryl, (iii) C_{7-13} aralkyl which may be substituted with halogen or C_{1-6} alkoxy, (iv) adamantyl or (v) C_{3-8} cycloalkyl.

(9) thienopyrimidylhydrazino which may be substituted with C_{1-6} alkyl.

Particularly, R^1 is preferably one of the following groups:

(1) C_{1-6} alkyl which may be substituted with (i) 2-thienyl or (ii) carboxyl, (2) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy or (iii) C_{1-6} alkylcarbamoylamino, (3) C_{7-13} aralkyl which may be substituted with nitro, (4) amino which may be substituted with (i) C_{1-6} alkyl, (ii) C_{6-12} aryl or (iii) C_{3-8} cycloalkyl, or (5) morpholino.

The symbol n may represent whichever of 1 and 2 but 2 is particularly preferred.

When n is 1, R^1 is preferably (1) C_{1-10} alkyl which may be substituted with cyano, (2) C_{2-12} alkinyl, (3) C_{1-8} cycloalkyl, (4) C_{6-12} aryl with may be substituted with (i) halogen, (ii) amino which may be substituted with carbamoyl with substituted with C_{1-6} alkyl, or (iii) C_{1-6} alkyl which may be substituted with halogen, or (5) pyrimidinyl.

The substituent at the 2-position is preferably one of the following groups (1)-(13).

(1) hydrogen.

(2) halogen.

(3) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of(i) amino which may be substituted with C_{7-19} aralkyl or C_{1-12} alkyl, (ii) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms which may be substituted with C_{6-14} aryl, (iii) phthalimido, (iv) C_{6-14} arylsulfonyl which may substituted with C_{1-12} alkyl, (v) hydroxyl which may be substituted with C_{1-12} alkanoyl, (vi) a 5- or 6-membered saturated nitrogen- and/or oxygen-containing heterocyclic group, (vii) halogen, (viii) C_{1-12} alkoxy-carbonyl, and (ix) a 5- to 6-membered unsaturated nitrogen- and/or oxgen-containing heterocyclic group which may be substituted with C_{1-6} alkyl or cyano.

(4) C_{2-12} alkenyl which may be substituted with C_{6-14} aryl.

(5) C_{6-14} aryl which may be substituted with C_{1-12} alkoxy.

(6) C_{7-19} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) C_{1-12} alkoxy, or (iv) halogen.

(7) C_{3-10} cycloalkyl.

(8) C_{3-10} cycloalkyl-C_{1-12} alkyl.

(9) a C_{4-12} bridged-ring hydrocarbon group.

(10) a 5- to 6-membered unsaturated nitrogen- and/or oxygen-containing heterocyclic group.
(11) C_{1-12} alkoxy.
(12) amino which may be substituted with (i) C_{1-12} alkyl which may substituted with C_{1-12} alkoxy-carbonyl or (b) a 5- or 6-membered nitrogen-containing heterocyclic group or (ii) C_{7-19} aralkyl.
(13) C_{1-12} alkoxy-carbonyl.
The substituent at the 2-position is more preferably one of the following groups (1) - (13).
(1) hydrogen.
(2) halogen.
(3) C_{1-6} alkyl which may be substituted with (i) amino which may be substituted with C_{7-13} aralkyl or C_{1-6} alkyl, (ii) 1-piperazinyl which may be substituted with C_{6-12} aryl, (iii) phthalimide, (iv) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, (v) hydroxyl which may be substituted with C_{1-6} alkanoyl, (vi) morpholino, (vii) piperidino, (viii) halogen, (ix) C_{1-6} alkoxy-carbonyl, and (x) oxazolyl which may be substituted with C_{1-6} alkyl or cyano.
(4) C_{2-6} alkenyl which may be substituted with C_{6-12} aryl.
(5) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy.
(6) C_{7-13} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) C1-6 alkoxy, or (iv) halogen.
(7) C_{3-8} cycloalkyl.
(8) C_{3-8} cycloalkyl-C_{1-6} alkyl.
(9) adamantyl.
(10) oxadiazolyl.
(11) C_{1-6} alkoxy.
(12) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with C_{1-6} alkoxy-carbonyl or pyridyl, or (ii) C_{7-13} aralkyl.

(13) C_{1-6} alkoxy-carbonyl.

Particularly, the substituent at the 2-position is preferably one of the following groups:

(1) hydrogen, (2) C_{1-6} alkyl which may be substituted with amino which may have C_{1-6} alkyl or C_{7-15} aralkyl substituent, (3) C_{3-6} cycloalkyl, (4) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy or (5) C_{7-13} aralkyl which may be substituted with (i) halogen or (ii) C_{1-6} alkoxy.

When a group bonded through a sulfinyl moiety exists at the 5-position, the preferred group at the 2-position is (1) C_{1-12} alkyl which may be substituted with C_{1-12} alkoxy-carbonyl, (2) C_{2-12} alkenyl which may be substituted with C_{6-14} aryl, (3) C_{6-14} aryl which may be substituted with C_{1-12} alkoxy, (4) C_{7-19} aralkyl, (5) C_{3-10} cycloalkyl, or (6) a 5- or 6-membered saturated nitrogen and/or sulfur containing heterocyclic group.

The substituent at the 4-position is preferably one of the following groups (1) - (12).

(1) cyano.

(2) C_{1-12} alkanoyl.

(3) carbamoyl which may be substituted with (i) C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{1-12} alkoxy or (iii) C_{7-19} aralkyl.

(4) a 5- or 6-membered saturated nitrogen-containing heterocyclic-carbonyl, which may be substituted with C_{6-14} aryl.

(5) thiocarbamoyl which may be substituted with (i) C_{1-12} alkyl or (ii) C_{7-19} aralkyl.

(6) a 5- or 6-membered saturated nitrogen-containing heterocyclic-thiocarbonyl.

(7) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of (i) hydroxyl which may be acylated with C_{6-14} arylcarbonyl, (ii)

halogen, (iii) carboxyl, (iv) cyano, (v) amino which may be substituted with C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group or C_{7-19} aralkyl, (vi) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms, which may be substituted with C_{6-14} aryl, (vii) phthalimido, (viii) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl, and (ix) C_{6-14} aryloxy which may be substituted with halogen,.

(8) C_{7-19} aralkyl which may be substituted with halogen or hydroxyl.

(9) a 5- or 6-membered nitrogen and sulfur-containing heterocyclic group, which may be substituted with (i) C_{1-12} alkoxy-carbonyl or (ii) C_{6-14} aryl.

(10) amino which may be substituted with C_{1-12} alkoxy-carbonyl.

(11) carboxyl.

(12) C_{1-12} alkoxy-carbonyl.

The substituent at the 2-position is more preferably one of the following groups (1) - (13).

(1) cyano.

(2) C_{1-6} alkanoyl.

(3) carbamoyl which may be substituted with (i) C_{1-6} alkyl which may be substituted with pyridyl, (ii) C_{7-13} aralkyl or (iii) C_{1-6} alkanoyl.

(4) piperidinocarbonyl.

(5) 1-piperazinylcarbonyl which may be substituted with C_{6-12} aryl.

(6) thiocarbamoyl which may be substituted with (i) C_{1-6} alkyl or (ii) C_{7-13} aralkyl.

(7) piperidinothiocarbonyl.

(8) C_{1-6} alkyl which may be substituted with (i) hydroxy which may be acylated with C_{6-12} arylcarbonyl, (ii) halogen, (iii) carboxyl, (iv) cyano, (v) amino which may substituted with (a) C_{1-6} alkyl which may be

substituted with pyridyl or (b) C_{7-13} aralkyl, (vi) 1-piperazinyl which may be substituted with C_{6-12} aryl, (vii) phthalimido, (viii) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, or (ix) C_{6-12} aryloxy which may be substituted with halogen.

(9) C_{7-13} aralkyl which may be substituted with halogen or hydroxyl.

(10) thiazolyl which may be substituted with C_{1-6} alkoxy-carbonyl or (b) C_{6-12} aryl.

(11) amino which may be substituted with C_{1-6} alkoxy-carbonyl.

(12) carboxyl.

(13) C_{1-6} alkoxy-carbonyl.

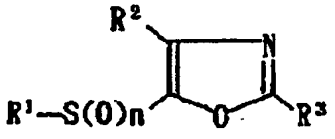
The more preferred substituent at the 4-position is cyano carbamoyl, thiocarbamoyl or C_{1-6} alkyl which may be substituted with halogen. Particularly preferred is cyano or thiocarbamoyl.

Where the substituent at the 5-position is a group bonded through a sulfinyl moiety, the substituent at the 4-position is preferably (1) cyano, (2) C_{1-12} alkyl which may be substituted with halogen or (3) thiocarbamoyl. Particularly preferred is cyano.

Compound (A) according to the present invention does not comprise the following compounds: (1) the compound having 4-methoxyphenyl or 4-methoxyphenylethinyl at the 2-position and nonafluorobutylsulfonyl at the 5-position, (2) the compound having phenyl at the 2-position and (2-phenyl-5-thiazolyl)sulfonyl at the 5-position, and (3) the compound having 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl at the 2-position and 4-methylphenylsulfonyl at the 5-position. Compound A according to the present invention is a novel compound.

Compound A for use in the present invention is

preferably a compound (I) of the following formula



(I)

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n represents 1 or 2; R^2 represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted, carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -S(O)m-R where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2; exclusive of the compounds in which R^2 is hydrogen and n is 2, wherein (1) R^3 is 4-methoxyphenyl or 4-methoxyphenylethinyl and R^1 is nonafluorobutyl, (2) R^3 is phenyl and R^1 is 5-(2-phenylthiazolyl), and (3) R^3 is 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl and R^1 is 4-methylphenyl.

Referring to the above formula (I), the hydrocarbon group which may be substituted, heterocyclic group which may be substituted, and amino which may be substituted for R^1 have the same meanings as defined hereinbefore.

The amino which may be substituted for R^3 may for

example be a group of the formula $-NR^4R^5$, wherein R^4 and R^5 independently represents hydrogen, a hydrocarbon group which may be substituted, or a heterocyclic group which may be substituted; R^4 and R^5 may be combined with the adjacent nitrogen atom to form a heterocyclic ring.

The acyl for R^2 may for example be a organic carboxylic acid-derived acyl group and is preferably an acyl group of 1-19 carbon atoms (C_{1-19} alkanoyl). To be specific, formyl, acetyl, ethylcarbonyl, propylcarbonyl, etc. can be mentioned. Particularly preferred are acyl groups of 1-6 carbon atoms (C_{1-6} alkanoyl).

The carbamoyl which may be substituted for R^2 may for example be a group of the formula $-CONR^6R^7$, where R^6 and R^7 independently represents hydrogen, acyl, a hydrocarbon group which may be substituted, or a heterocyclic group which may be substituted; R^6 and R^7 may be combined with the adjacent nitrogen atom to form a heterocyclic ring.

The thiocarbamoyl which may be substituted for R^2 may for example be a group of the formula $-CS-NR^6R^7$ wherein R^6 and R^7 independently represents hydrogen, a hydrocarbon group which may be substituted, or a heterocyclic group which may be substituted; R^6 and R^7 may be combined with the adjacent nitrogen atom to form a heterocyclic ring.

The carboxyl which may be esterified for R^2 or R^3 may for example be a group of the formula $-COOR^{10}$, where R^{10} represents hydrogen, a hydrocarbon group which may be substituted, or a heterocyclic group which may be substituted.

The substituent for amino which may be substituted for R^2 may for example be C_{1-12} alkoxy-carbonyl (preferably C_{1-6} alkoxy-carbonyl). Particularly

preferred is buthoxycarbonyl.

The halogen for R^3 may for example be fluorine, chlorine, bromine, or iodine.

The hydrocarbon-oxy which may be substituted may for example be a group of the formula $-OR^{11}$, where R^{11} represents a hydrocarbon group which may be substituted.

The "hydrocarbon group which may be substituted" for R, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, or R^{11} can be the same as the "hydrocarbon group that may be substituted" which has been defined for R^1.

The "heterocyclic group which may be substituted" for R, R^2, R^3, R^4, R^5, R^6, R^7, or R^{10} can be the same as the "heterocyclic group that may be substituted" which has been defined for R^1.

The heterocyclic group which R^4 and R^5, or R^6 and R^7, may be combined with the adjacent nitrogen atom to form a heterocyclic group, can be the same as heterocyclic group formed by R^d and R^e which may be combined with the adjacent nitrogen atom.

The acyl for R^6 or R^7 can be the same as the acyl which has been defined for R^2.

$-S(O)m-R$ for R^3 includes C_{1-12} alkylthio (e.g. methylthio, ethylthio, etc.), C_{6-14} arylthio (e.g. phenylthio etc.), C_{6-14} aryl-C_{1-6} alkylthio (e.g. benzylthio etc.), C_{1-14} alkylsulfinyl (e.g. methylsulfinyl, ethylsulfinyl, etc.), C_{6-14} arylsulfinyl (e.g. phenylsulfinyl etc.), C_{6-14} aryl-C_{1-6} alkylsulfinyl (e.g. benzylsulfinyl etc.), C_{1-12} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.), C_{6-14} arylsulfonyl (e.g. phenylsulfonyl etc.), C_{6-14} aryl-C_{1-6} alkylsulfonyl (e.g. benzylsulfonyl etc.), etc.

Referring to the above formula (I), R^1 may be the same as R^1 of the group of the formula $R^1-S(O)n-$ at the

5-position described above. R^2 may be the same as the substituent at the 4-position described above. R^3 may be the same as the substituent at the 2-position described above.

As compound (I) of the present invention, all the compounds corresponding to the above combinations of R^1, R^2 and R^3 are invariably preferred.

Compound (I) of the present invention does not include compounds such that R^2 is hydrogen and n is equal to 2, wherein (1) R^3 is 4-methoxyphenyl or 4-methoxyphenylethinyl and R^1 is nonafluorobutyl, (2) R^3 is phenyl and R^1 is 4-(2-phenylthiazolyl), (3) R^3 is 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl and R^1 is 4-methylphenyl. Compound (I) is a novel compound.

Compound B for use in the present invention is an oxazole derivative having a group bonded through a sulfinyl (-SO-) or sulfonyl ($-SO_2-$) moiety at the 5-position of the oxazole ring.

The 2-position of the oxazole ring may be unsubstituted but may be substituted by a certain group such as halogen or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom.

The 4-position of the oxazole ring may be unsubstituted but may be substituted by a certain group such as halogen or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom.

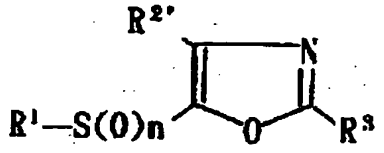
The substituent group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring may be the same as the group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring of compound A.

The halogen atom or the group bonded through a carbon, nitrogen, oxygen, or sulfur atom at the 2- or

4-position of the oxazole ring may be the same as the halogen atom or the group bonded through a carbon, nitrogen, oxygen, or sulfur atom at the 2- or 4-position of compound A mentioned hereinbefore.

Compound B for use in the present invention includes the specific compounds excluded from compound A, namely the compounds having hydrogen at the 4-position wherein (1) the substituent at the 2-position is 4-methoxyphenyl or 4-methoxyphenylethinyl and the substituent at the 5-position is nonafluorobutylsulfonyl, (2) the substituent at the 2-position is phenyl and the substituent at the 5-position is (2-phenyl-5-thiazolyl)sulfonyl, and (3) the substituent at the 2-position is 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl and the substituent at the 5-position is 4-methylphenylsulfonyl.

Compound B is preferably a compound of the formula



(I')

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n represents 1 or 2; $R^{2'}$ represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted or carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino

which may be substituted, carboxyl which may be esterified or a group of the formula -S(O)m-R, where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2.

In the above formula (I'), R^1 and R^3 are as defined hereinbefore; $R^{2'}$ has the same meaning as R^2 defined hereinbefore.

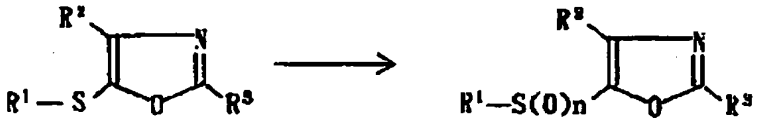
Referring to compound A or B according to the present invention, where it has an acidic group (e.g. carboxyl, phenolic hydroxy, sulfo, etc.) or a basic group (e.g. amino) as a substituent, the compound may form a salt with a suitable base or acid, and these salts are included in the compound of the invention. The kind of salt is preferably a pharmacologically acceptable salt, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids. The salt with an inorganic base includes alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), and ammonium salts. The salt with an organic base includes salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, dicyclohexylamine, etc. The salt with an inorganic acid includes salts with hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid, etc. The salt with an organic acid includes salts with formic acid, acetic acid, oxalic acid, fumaric acid, maleic acid, succinic acid, citric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. The salt with a basic amino acid includes salts with arginine, lysine, ornithine, etc. The salt with an acidic amino acid includes salts with aspartic acid, glutamic acid, etc.

[Best Mode for Carrying Out the Invention]

Compound A of the present invention can be produced generally in the same manner as compound (I) of the invention which is described in detail below.

Compound (I) of the present invention can be produced typically by the following processes (1)-(4).

(1)



(II) (I)

wherein R^1, R^2, R^3, and n are as defined hereinbefore.

This process comprises oxidizing the oxazole derivative (II) to compound (I) of the invention. More particularly, the derivative (II) is dissolved in a solvent and reacted with an oxidizing agent to give compound (I).

The oxidizing agent that can be used includes but is not limited to m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, and halogen. The amount of the oxidizing agent is generally about 1-3 moles per mole of compound (II). Specifically, the oxidizing agent is used in a proportion of generally about 1-1.5 moles and preferably about 1-1.2 moles when n=1 or generally about 2-3 moles and preferably about 2-2.5 moles when n=2.

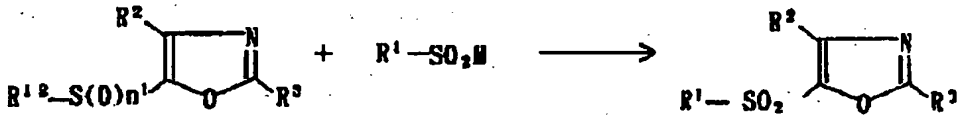
The reaction solvent need not be critically chosen unless it reacts with the oxidizing agent used. Thus, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-

dichloroethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., aliphatic hydrocarbons such as pentane, hexane, petrolen, ether, etc., alcohols such as methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc., carboxylic acids such as acetic acid, trifluoroacetic acid, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, water, and mixtures thereof can be mentioned.

This oxidation reaction can be conducted in the presence of a catalyst such as vanadium pentoxide, benzeneselenic acid, ruthenium oxide, osmium oxide, or the like. While this reaction may be carried out under cooling, at room temperature, or under heating, it is usually conducted at room temperature or under heating. The reaction time is generally about 1-20 hours and preferably about 1-10 hours.

After the reaction, the objective compound of high purity can be isolated by subjecting the reaction mixture to a known purification procedure such as solvent extraction, distillation, column chromatography, and recrystallization.

(2)



(III) (IV) (I :n=2)

wherein R^1, R^2, R^3, and n are as defined hereinbefore; R^{12} represents lower alkyl or phenyl; n^1 represents 0, 1, or 2; M represents an alkali metal.

The alkali metal for M in the above formula, may for example be lithium, sodium, potassium, or cesium.

The lower alkyl for R^{12} includes C_{1-6} alkyl groups such as methyl, ethyl, propyl, etc.

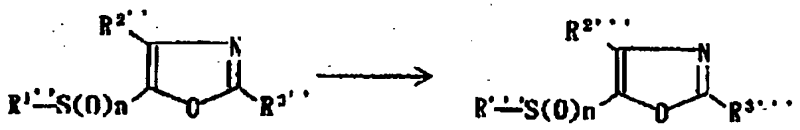
This process comprises reacting oxazole derivative (III) with sulfinic acid salt (IV) in a solvent to give compound (I) in which n=2.

The reaction solvent is preferably a polar solvent. Thus, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., alcohols such as methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc., acetone, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoramide, water, and mixtures thereof can be employed.

This reaction is conducted under cooling, at room temperature, or under heating and the reaction time is generally about 1-20 hours and preferably about 1-10 hours.

After the reaction, the objective compound of high purity can be isolated by subjecting the reaction mixture to a known procedure such as solvent extraction, distillation, column chromatography, and recrystallization.

(3)



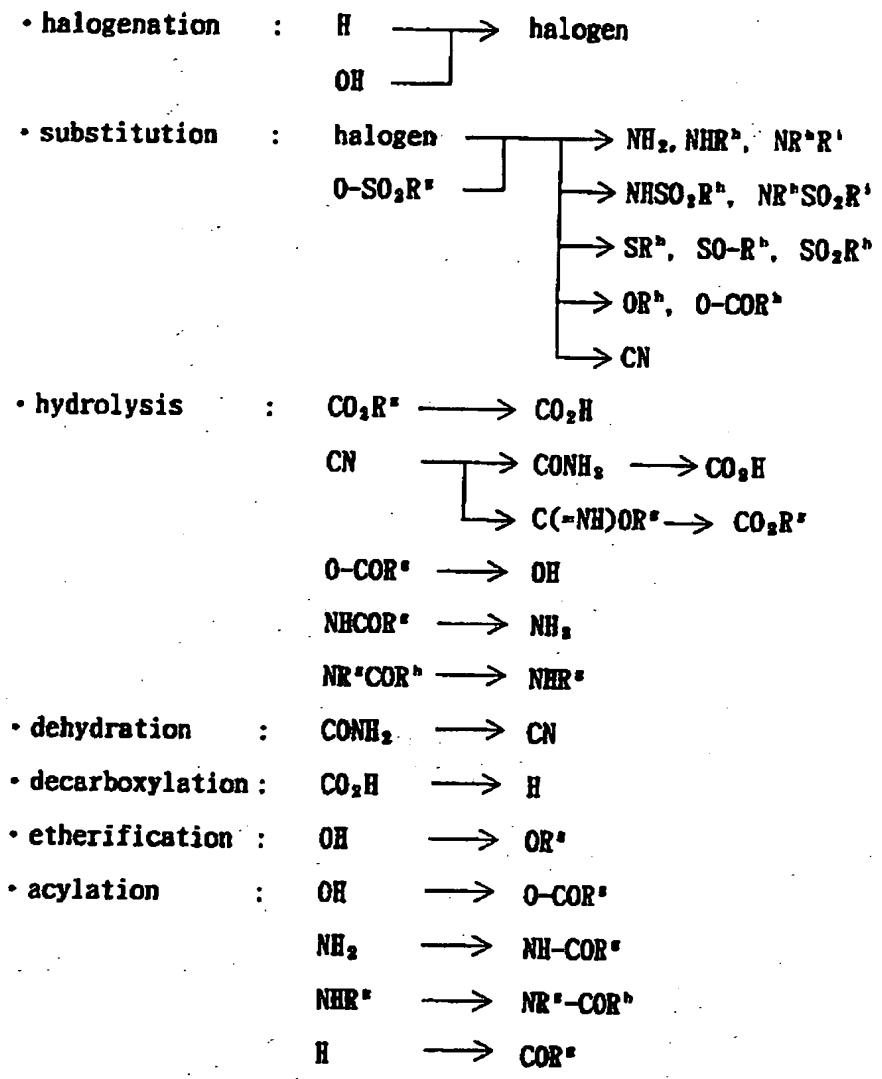
(I'') (I''')

wherein $R^{1''}$, $R^{2''}$, and $R^{3''}$ have the same respective meanings as R^1, R^2, and R^3 defined above. $R^{1'''}$, $R^{2'''}$, and $R^{3'''}$ have the same respective meanings as R^1, R^2, and R^3 defined above. $R^{1''}$ and $R^{1'''}$, $R^{2''}$ and $R^{2'''}$, and $R^{3''}$ and $R^{3'''}$ may respectively be the same but at least one of the three pairs consists of dissimilar groups.

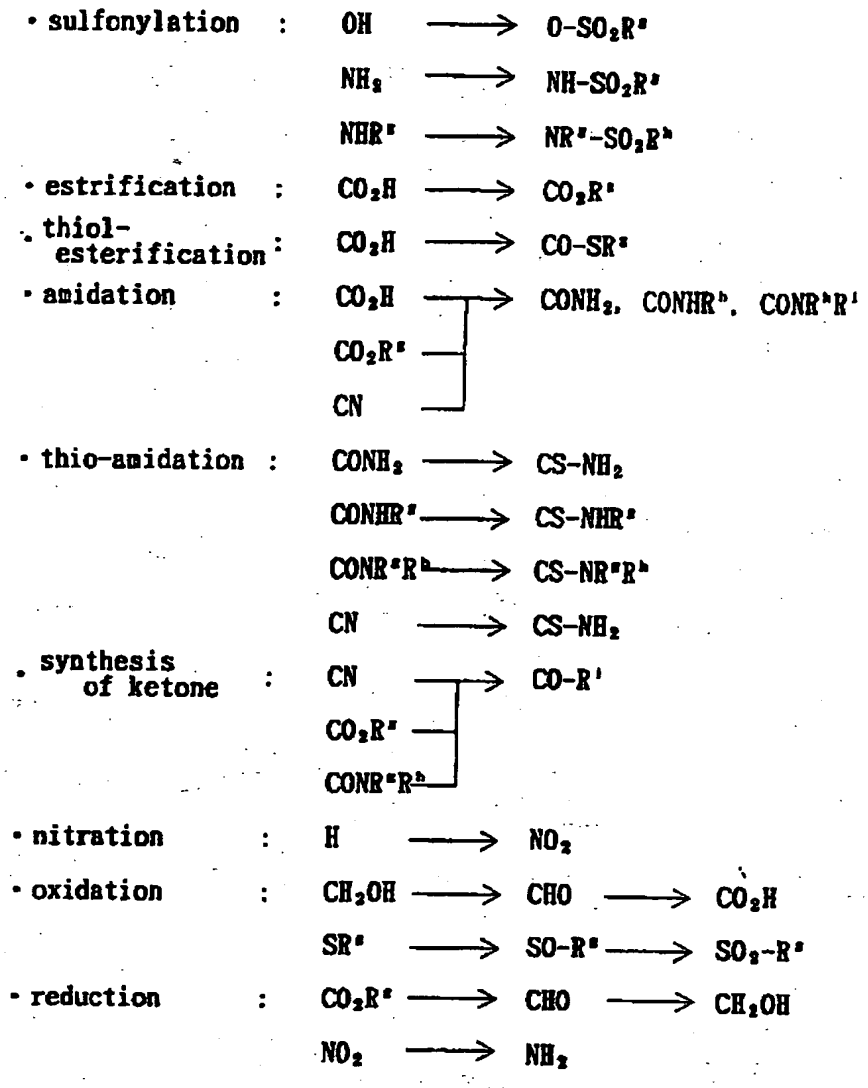
In this process, compound (I''') is produced by

substituting 1-3 of $R^{1'}$, $R^{2'}$ and $R^{3'}$ of oxazole derivative (I'') or subjecting (I'') to functional transformation. The substitution reaction and functional transformation reaction can be carried out by the routine procedures. As such routine procedures, the following methods can be typically mentioned.

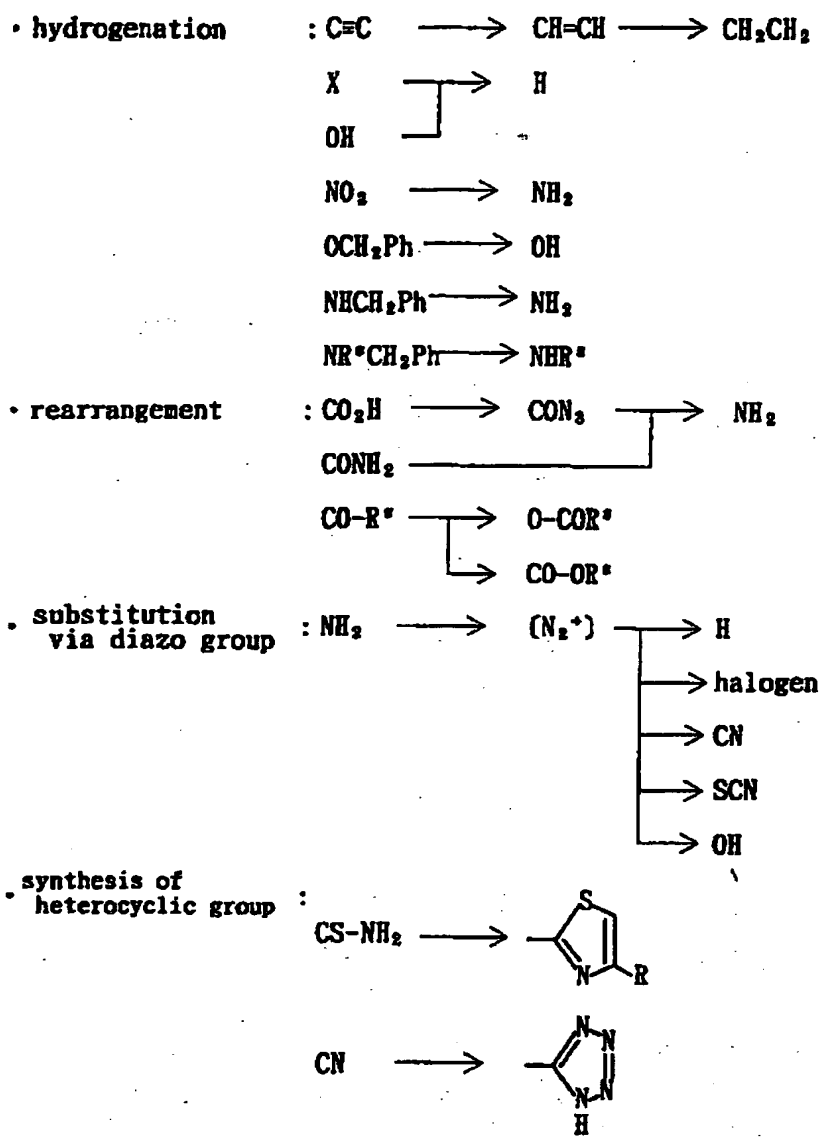
[Table 1]


• halogenation : H → halogen
OH
• substitution : halogen → NH2, NHRb, NRbR'
O-SO2Rg → NHSO2Rb, NRbSO2R'
→ SRb, SO-Rb, SO2Rb
→ ORb, O-CORb
→ CN
• hydrolysis : CO2Rg → CO2H
CN → CONH2 → CO2H
→ C(=NH)ORg → CO2Rg
O-CORg → OH
NHCORg → NH2
NRgCORb → NHRg
• dehydration : CONH2 → CN
• decarboxylation : CO2H → H
• etherification : OH → ORg
• acylation : OH → O-CORg
NH2 → NH-CORg
NHRg → NRg-CORb
H → CORg

[Table 2]

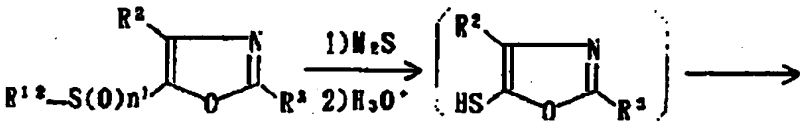

• sulfonylation :
OH → O-SO2Ra
NH2 → NH-SO2Ra
NHRa → NRa-SO2Rb
• estrification :
CO2H → CO2Ra
• thiol-esterification :
CO2H → CO-SRa
• amidation :
CO2H → CONH2, CONHRb, CONRbR1
CO2Ra → CONH2, CONHRb, CONRbR1
CN → CONH2, CONHRb, CONRbR1
• thio-amidation :
CONH2 → CS-NH2
CONHRa → CS-NHRa
CONRaRb → CS-NRaRb
CN → CS-NH2
• synthesis of ketone :
CN → CO-R1
CO2Ra → CO-R1
CONRaRb → CO-R1
• nitration :
H → NO2
• oxidation :
CH2OH → CHO → CO2H
SRa → SO-Ra → SO2-Ra
• reduction :
CO2Ra → CHO → CH2OH
NO2 → NH2

[Table 3]

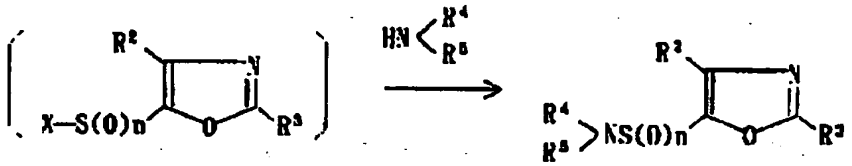

• hydrogenation
: C≡C → CH=CH → CH2CH2
X → H
OH
NO2 → NH2
OCH2Ph → OH
NHCH2Ph → NH2
NR'CH2Ph → NHR'
• rearrangement
: CO2H → CON3 → NH2
CONH2
CO-R' → O-COR'
CO-OR'
• substitution via diazo group
: NH2 → (N2+) → H
halogen
CN
SCN
OH
• synthesis of heterocyclic group
CS-NH2
S
N
R
CN
N
N
N
N
H

Wherein R^g, R^h, and R^i independently represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

(4)



(III) (V)



(VI) (VII)

wherein R^1, R^2, R^3, R^{12}, R^4, R^5, n, and M are as defined hereinbefore; X represents a leaving group.

For X in the above formula, halogen such as chlorine, bromine, iodine, etc., p-toluenesulfonyloxy, or methanesulfonyloxy, for instance, is employed. Among them, halogen is preferred and chlorine is particularly suitable.

This process is directed to production of compound (VII), which is a species of compound (I) of the invention wherein R^1 represents $-NR^4R^5$. More specifically, the process comprises reacting compound (III) with M_2S, e.g. sodium sulfide or potassium sulfide, treating the reaction product with an acid to give a thiol intermediate (V), transforming (V) to an intermediate compound (VI) in the per se known method (Chem. Lett., 1992, p.1483), and reacting (VI) further with a primary or secondary amine in the presence of a base to give compound (VII). In this process, the intermediates (V) and (VI) can be respectively isolated

and purified but this is not essential.

The reaction solvent for use in the reaction with M_2S in the above course of synthesis from compound (III) to compound (V) is preferably a polar solvent, e.g. halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., alcohols such as methanol, ethanol, isopropyl alcohol, etc., acetone, acetonitrile, water, and mixture of such solvents.

This reaction is conducted under cooling, at room temperature, or under heating, and the reaction time is generally about 1-20 hours and preferably about 1-10 hours.

There is no particular limitation on the acid that can be used in the acid treatment but generally an aqueous solution of hydrochloric acid, sulfuric acid, nitric acid, acetic acid, or the like is employed.

The course of synthesis from compound (III) to compound (V) can be carried out using MSH, e.g. sodium hydrosulfide or potassium hydrosulfide, instead of M_2S. While this reaction can be conducted under the same conditions as the reaction using M_2S, the subsequent acid treatment is unnecessary.

The course of synthesis from compound (V) to compound (VI) can be carried out by the known procedure using sulfuryl chloride and a salt of nitric acid as described hereinbefore.

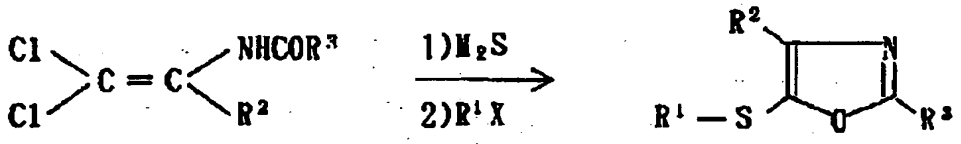
The base that can be used in the course of synthesis from compound (VI) to compound (VII) includes sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, pyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, and sodium amide, among others. The reaction solvent that can be used includes but is not limited to hydrogenated hydrocarbons such as

dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., aliphatic hydrocarbons such as pentane, hexane, petroleum ether, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. This reaction is conducted under cooling, at room temperature, or under heating and the reaction time is generally about 1-20 hours and preferably about 1-10 hours.

After the reaction, the objective compound of high purity can be isolated from the reaction mixture by the known procedures such as solvent extraction, distillation, column chromatography, and recrystallization.

The starting compound (II) for use in process (1) can be produced by the known technology or any method analogous thereto. The known technology includes the process starting with 2-amino-3,3-dichloroacrylonitrile, in which the starting compound is converted to a 3,3-bis(substituted mercapto)derivative which, in turn, is cyclized with a silver salt [Matsumura et al., Chem. Pharm. Bull. 24, p.912 (1976), ditto, p.948] and the process in which 5-mercapto-oxazole is S-alkylated [T. K. Vinogradova et al., Zh. Org. Khim. 18, 1864 (1982)].

The starting compound (II) can be obtained by the following process.



(VIII) (II)

wherein R^1, R^2, R^3, and M are as defined hereinbefore; X

represents a leaving group.

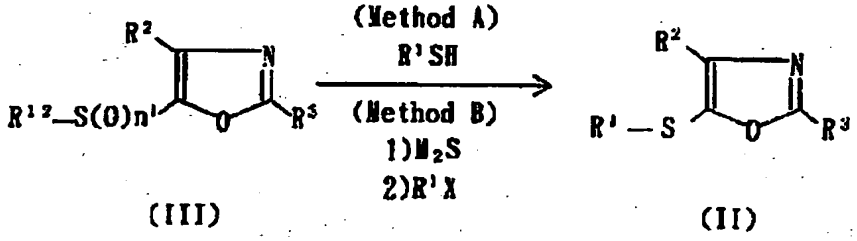
Referring to the above formula, R^2 is preferably an electron-withdrawing group such as cyano, alkyloxycarbonyl, carbamoyl, or the like.

X preferably represents halogen, e.g. chlorine, bromine, or iodine, p-toluenesulfonyloxy, or methanesulfonyloxy, for instance.

In this process, the compound (VIII) obtained by the process of Matsumura et al. [Chem. Pharm. Bull. 24, p.912 (1976)] or any process analogous thereto is reacted with M_2S, such as sodium sulfide or potassium sulfide, in a solvent, and then treated with R_3X to give compound (II).

The reaction solvent is preferably a polar solvent. Thus, for example, hydrogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., alcohols such as methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc., acetone, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoramide, etc., water, and mixtures thereof can be employed. This reaction is conducted under cooling, at room temperature, or under heating and the reaction time is generally about 1-20 hours and preferably about 1-10 hours.

The starting compound (II) can also be produced by the following process.



(III) (II)

wherein R^1, R^2, R^3, R^{12}, n^1, M, and X are respectively as defined hereinbefore.

Thus, in a solvent, compound (III) is reacted with a thiol in the presence of a base (process A) or first reacted with M_2S, e.g. sodium sulfide or potassium sulfide, and then treated with R_3X (process B) to give compound (II). For both processes A and B, the reaction solvent is preferably a polar solvent, e.g. halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc., alcohols such as methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc., acetone, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoramide, etc., water, and mixtures thereof. The reaction is conducted under cooling, at room temperature, or under heating and the reaction time is generally about 1-20 hours and preferably 1-10 hours.

The base that can be used in process A includes but is not limited to sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, pyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, and sodium amide. It is also possible to treat the thiol with a base and subject the resulting thiol anion (RS^-) to the reaction with compound (III).

Compound (II) thus obtained can be converted to compounds having different substituent groups by introducing desired substituent groups for 1-3 of its substituents R^1, R^2, and R^3 by the same procedure as described in connection with process (3) for producing compound (I) or subjecting it to functional transformation.

Among species of starting compound (III) for use in processes (2) and (4), the compound in which $n^1=0$ is subsumed in the category of said compound (II) and the compound in which $n^1=1$ and 2 is subsumed in the

category of compound (I). Therefore, these compounds can be produced by procedures corresponding to the above production processes.

The starting compound (I'') for process (3) can be produced by process (1) or (2).

In this manner, the oxazole derivative (I) of the present invention can be provided.

Referring to the formula (I), desirably R^1 represents 1) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,

(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ independently represents (A) hydrogen, (B) a C_{1-19} hydrocarbon group which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k)

carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl, (C) a heterocyclic group which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k) carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl, or (D) $-SO_2R^{f'}$, wherein $R^{f'}$ represents a C_{1-19} hydrocarbon group which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c)

halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k) carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl; $R^{d'}$ and $R^{e'}$ may be combined with the adjacent nitrogen atom to form a heterocyclic group selected from 1-pyrrolidinyl, 1-imidazolyl, piperidino, 1-piperazinyl, 3-oxazolidinyl, hexamethylenimino, heptamethylenimino, morpholono, 1-indolinyl and phthalimido, which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k) carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12}

alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
2) a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-}

$_8$ cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,

(12) C_{1-12} alkanoyl,

(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b)

C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h)

C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

3) $-NR^{4'}R^{5'}$, wherein $R^{4'}$ and $R^{5'}$ independently represents (A) hydrogen, (B) a $_{1-19}$ hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,

(12) C_{1-12} alkanoyl,

(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6}

alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(C) a 5- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12}

alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl; $R^{4'}$ and $R^{5'}$ may be combined with the adjacent nitrogen atom to form a heterocyclic group selected from 1-pyrrolidinyl, 1-imidazolyl, piperidino, 1-piperazinyl, 3-oxazolidinyl, hexamethylenimino, heptamethylenimino, morpholono, 1-indolinyl and phthalimido, which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi)

carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k) carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl,

4) $-NR^{a'}-CO-R^{b'}$, wherein $R^{a'}$ and $R^{b'}$ independently represents (A) hydrogen, (B) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(C) a 5- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12}

alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

5) $-NR^{a'}-CO-NR^{4'}R^{5'}$, wherein $R^{a'}$, $R^{4'}$ and $R^{5'}$ have the same meanings as defined above,

6) $-NR^{a'}-CS-NR^{4'}R^{5'}$, wherein $R^{a'}$, $R^{4'}$ and $R^{5'}$ have the same meanings as defined above,

7) $-NR^{a'}-NR^{4'}R^{5'}$, wherein $R^{a'}$, $R^{4'}$ and $R^{5'}$ have the same meanings as defined above, or
8) $-NR^{a'}-CO-OR^{b'}$, wherein $R^{a'}$ and $R^{b'}$ have the same meanings as defined above;
R^2 represents 1) hydrogen, 2) cyano, 3) organic carboxylic acid-derived acyl, 4) $-CONR^{6'}R^{7'}$, wherein $R^{6'}$ and $R^{7'}$ independently represents (A) hydrogen, (B) C_{1-12} alkanoyl, (C) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6}

alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl,

or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(D) a 5- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e)

hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,

(12) C_{1-12} alkanoyl,

(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12}

alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl; $R^{6'}$ and $R^{7'}$ may be combined with the adjacent nitrogen atom to form a heterocyclic group selected from 1-pyrrolidinyl, 1-imidazolyl, piperidino, 1-piperazinyl, 3-oxazolidinyl, hexamethylenimino, heptamethylenimino, morpholono, 1-indolinyl and phthalimido, which may be substituted with (a) C_{1-4} alkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-

carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (b) C_{3-8} cycloalkyl which may be substituted with (i) C_{3-8} cycloalkyl, (ii) halogen, (iii) cyano, (iv) hydroxyl, (v) C_{1-4} alkoxy, (vi) carboxyl, (vii) C_{1-4} alkoxy-carbonyl, (viii) nitro, (ix) amino, (x) carbamoyl, or (xi) C_{1-4} alkanoyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-4} alkoxy, (g) carboxyl, (h) C_{1-4} alkoxy-carbonyl, (i) nitro, (j) di-C_{1-4} alkylamino, (k) carbamoyl, (l) C_{1-4} alkanoyl, (m) C_{6-12} aryl which may be substituted with (i) C_{1-4} alkyl, (ii) C_{3-8} cycloalkyl, (iii) halogen, (iv) cyano, (v) hydroxyl, (vi) C_{1-4} alkoxy, (vii) carboxyl, (viii) C_{1-4} alkoxy-carbonyl, (ix) nitro, (x) amino, (xi) carbamoyl, or (xii) C_{1-4} alkanoyl, or (n) 2-pyridyl,

5) $-CSNR^{6'}R^{7'}$, wherein $R^{6'}$ and $R^{7'}$ have same meanings as defined above,

6) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-

carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,

(12) C_{1-12} alkanoyl,

(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

7) a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e)

C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl,

(f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k)

carbamoyl or (l) C_{1-6} alkanoyl,
8) amino which may be substituted with a C_{1-19} hydrocarbon-oxy, or
9) carboxyl which may be esterified;
R^3 represents 1) hydrogen, 2) halogen, 3) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl, (2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl, (3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl, (6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (1) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (1)

C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano,

(e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

4) a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{1-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d)

hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

5) a C_{1-19} hydrocarbon-oxy which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings

as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
6) $-NR^{4'}R^{5'}$, wherein $R^{4'}$ and $R^{5'}$ have the same meanings as defined above,
7) carboxyl which may be esterified,

8) or a group of the formula -S(O)m-R", where R" represents (A) a C_{1-19} hydrocarbon group which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(3) halogen
(4) cyano,
(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,
(6) C_{1-12} alkoxy,
(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(8) carboxyl,
(9) C_{1-12} alkoxy-carbonyl,
(10) nitro,
(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d)

cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,

(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or

(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or (B) a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur which may be substituted with (1) C_{1-12} alkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(2) C_{3-8} cycloalkyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(3) halogen

(4) cyano,

(5) hydroxyl which may be acylated with (a) C_{1-12} alkanoyl, (b) C_{6-14} arylcarbonyl or (c) C_{7-19} aralkanoyl,

(6) C_{1-12} alkoxy,

(7) C_{6-14} aryloxy which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,

(8) carboxyl,

(9) C_{1-12} alkoxy-carbonyl,

(10) nitro,

(11) carbamoyl which may be substituted with C_{1-12} alkyl,
(12) C_{1-12} alkanoyl,
(13) C_{6-14} aryl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(14) C_{6-14} arylcarbonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(15) a 3- to 8-membered heterocyclic group containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, or a condensed heterocyclic group thereof with a 6- to 8-membered carbocyclic group or a heterocyclic group, which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(16) $-NR^{d'}R^{e'}$, wherein $R^{d'}$ and $R^{e'}$ have the same meanings as defined above,
(17) C_{1-12} alkylthio which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(18) C_{1-12} alkylsulfinyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,

(19) C_{1-12} alkylsulfonyl which may be substituted with (a) C_{3-8} cycloalkyl, (b) halogen, (c) cyano, (d) hydroxyl, (e) C_{1-12} alkoxy, (f) carboxyl, (g) C_{1-12} alkoxy-carbonyl, (h) nitro, (i) amino, (j) carbamoyl, or (k) C_{1-12} alkanoyl,
(20) C_{6-14} arylthio which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl,
(21) C_{6-14} arylsulfinyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl, or
(22) C_{6-14} arylsulfonyl which may be substituted with (a) C_{1-6} alkyl, (b) C_{3-8} cycloalkyl, (c) halogen, (d) cyano, (e) hydroxyl, (f) C_{1-6} alkoxy, (g) carboxyl, (h) C_{1-6} alkoxy-carbonyl, (i) nitro, (j) amino, (k) carbamoyl or (l) C_{1-6} alkanoyl; m represents 0, 1, or 2.

[Industrial Application]

Compound B, particularly compound A, has excellent inhibitory activities of IL-6 activity and NO production of NOS inducible cells and low toxicity. Therefore, it can be used as a safe inhibitor of IL-6 activity or NO production in human and other mammalian animals (e.g. mouse, rat, guinea pig, rabbit, dog, cat, bovine, swine, sheep, monkey, chimpanzee, etc.). Furthermore, compound B can be safely used as a drug, for example a prophylactic and a therapeutic drug for IL-6-associated diseases, namely heart diseases such as myocardiopathy, cardiac hypertrophy, myocardial infarction, angina pectoris, etc., various autoimmune diseases such as chronic rheumatoid arthritis, systemic

lupus erythematosus, systemic scleroderma, rheumatic fever, polymyositis, periarteritis nodosa, Sjögren's syndrome, Behcet's disease, Castleman's disease, autoimmune hemolytic anemia, etc., inflammatory diseases such as mesangial proliferative nephritis, IgA nephritis, lupus nephritis, osteoporosis, amyloidosis, bronchial asthma, atopic dermatitis, psoriasis, pleurisy, ulcerative colitis, atherosclerosis, active chronic hepatitis, alcoholic cirrhosis, gout, various types of encephalitis, etc., or diseases accompanied by granuloma such as multiple myeloma, atrial myxoma, renal carcinoma, pulmonary adenocarcinoma, malignant mesothelioma, ovarian cancer, cancerous cachexia, etc. or NO-associated diseases, for example, atherosclerosis, myocarditis, myocardiopathy, ischemic brain disorder, Alzheimer's disease, multiple sclerosis, septicemia, rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerulonephritis, osteoporosis, pneumonia, hepatitis, graft rejection, pain, etc., in human and other mammalian animals (e.g. mouse, rat, guinea pig, rabbit, dog, cat, bovine, swine, sheep, monkey, chimpanzee, etc.).

For use as a drug, compound B can be administered, either alone or in mixture with a pharmacologically acceptable carrier, excipient, or diluent, orally in such dosage forms as tablets, capsules, granules, powders, etc. or parenterally in such dosage forms as injections, among other forms.

For the manufacture of oral dosage forms, taking tablets as an example, binders (e.g hydroxypropyl-cellulose, hydroxypropylmethylcellulose, macrogols, etc.), disintegrators (e.g. starch, carboxymethylcellulose calcium, etc.), excipients (e.g. lactose, talc, etc.), and lubricants (e.g. magnesium stearate, talc, etc.) can be suitably formulated.

For the manufacture of parenteral products, taking an injection as an example, an aqueous medium (e.g. distilled water), isotonic solutions (e.g. saline, Ringer's solution), isotonizing agents (e.g. glucose, D-sorbitol, D-mannitol, sodium chloride, etc.), stabilizers (e.g. human serum albumin etc.), antiseptics (e.g. benzyl alcohol, chlorobutanol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, phenols, etc.), buffers (e.g. phosphate buffer, sodium acetate buffer, etc.), and local anesthetics (e.g. benzalkonium chloride, procaine hydrochloride, etc.) can be suitably formulated.

The daily dosage of compound B depends on various factors such as species of mammals, diseases, clinical condition, etc. For the usual daily oral dosage, about 1-100 mg, preferably about 1-50 mg, per kg body weight of both human and mammalian animals, is administered in 1-3 divided doses. For administration by routes other than peroral, about 0.1-10 mg, preferably about 0.1-5 mg, per kg body weight is administered once daily.

The following reference examples, examples, and experimental examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention.

The compounds obtained in Reference Examples and Examples are shown in Table 4 - Table 25. The IR spectra were recorded by the liquid film method or the KBr disk method. In the table, Ph represents phenyl.

[Reference Example 1]

3,3-Dichloro-2-hexanoylaminoacrylonitrile

In accordance with the method of Matsumura et al. [Chem. Pharm. Bull., 24, 924, (1976)], 50.0 g of 2-amino-3,3-dichloroacrylonitrile was reacted with 84.9 g of hexanoic anhydride using 0.5 ml of concentrated sulfuric acid as an acid catalyst to provide 81.4 g of the title compound as crude crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, J=7.0 Hz, 3H), 1.25-1.45 (m, 4H), 1.55-1.85 (m, 2H), 2.35 (t, J=7.5 Hz, 2H), 6.83 (bs, 1H).

In the same manner, the compound of Reference Example 5 was synthesized.

[Reference Example 2]

2-Benzoylamino-3,3-dichloroacrylonitrile

In 100 ml of dichloromethane was dissolved 5.00 g of 2-amino-3,3-dichloroacrylonitrile, and under ice-cooling, 5.64 g of benzoyl chloride and 5.36 g of anhydrous aluminum chloride were added in the order mentioned. The mixture was stirred at 0°C for 1 hour. This reaction mixture was diluted with 200 ml of water and extracted with 3 portions of dichloromethane. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: dichloromethane) and recrystallized from dichloromethane/n-hexane to provide 4.45 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 7.43-7.70 (m, 4H), 7.84 (d, 2H).

Elemental analysis (%) (for $C_{10}H_6N_2OCl_2$)

Calcd.: C, 49.82; H, 2.51; N, 11.62

Found : C, 49.97; H, 2.27; N, 11.70

In the same manner, the compounds of Reference Examples 3 and 4 were synthesized.

[Reference Example 6]

3,3-Dichloro-2-methoxycarbonylaminoacrylonitrile

To 200 ml of methyl chloroformate was added 20.0 g

of 2-amino-3,3-dichloroacrylonitrile and the mixture was refluxed for 48 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate/n-hexane to provide 23.7 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 3.83 (s, 3H), 6.26 (bs, 1H).

Elemental analysis (%) (for $C_5H_4N_2O_2Cl_2$)

Calcd.: C, 30.80; H, 2.07; N, 14.37

Found : C, 30.71; H, 2.14; N, 14.30

[Reference Example 7]

Butyl N'-(1-cyano-2,2-dichlorovinyl)ureidoacetate

In the same manner as Reference Example 2, 20.37 g of anhydrous aluminum chloride was permitted to act upon 20.92 g of 2-amino-3,3-dichloroacrylonitrile and 24.0 g of butyl isocyanatoacetate to provide 23.6 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H), 1.25-1.48 (m, 2H), 1.56-1.73 (m, 2H), 4.05 (d, 2H), 4.17 (t, 2H), 6.12 (t, 1H), 7.21 (bs, 1H).

Elemental analysis (%) (for $C_{10}H_{13}N_3O_3Cl_2$)

Calcd.: C, 40.83; H, 4.45; N, 14.29

Found : C, 40.64; H, 4.55; N, 14.25

[Reference Example 8]

2-Acetylamino-3,3-bis(pentylthio)acrylonitrile

According to the method of Matsumura et al. [Chem. Pharm. Bull., 24, 948, (1976)], 2.00 g of 2-acetylamino-3,3-dichloroacrylonitrile was reacted with 2.56 g of pentanethiol to provide 3.44 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, J=7.3 Hz, 6H), 1.15-1.50 (m, 8H), 1.50-1.75 (m, 4H), 2.14 (s, 3H), 2.85 (t, J=7.4 Hz, 2H), 2.91 (t, J=7.5 Hz, 2H), 7.30 (bs, 1H).

Elemental analysis (%) (for $C_{15}H_{26}N_2OS_2$)

Calcd.: C, 57.28; H, 8.33; N, 8.91

Found : C, 57.06; H, 8.36; N, 8.67

In the same manner, the compounds of Reference Examples 9-13 and 16 were synthesized.

[Reference Example 14]

3,3-Bis(methylthio)-2-chloroacetylaminoacrylonitrile

To a solution of 2-amino-3,3-bis(methylthio)acrylonitrile (9.98 g) in 100 ml of dichloromethane was added 7.39 g of chloroacetyl chloride and the mixture was stirred under ice-cooling for 10 minutes. Then, 8.72 g of aluminum chloride was added and the mixture was further stirred at room temperature for 1 hour. To this reaction mixture was added iced water to stop the reaction and the organic layer was washed with 3 portions of cold water. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 3/1) and recrystallized from dichloromethane/n-hexane (1:2) to provide 8.86 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 2.48 (s, 3H), 4.17 (s, 2H), 8.23 (bs, 1H).

Elemental analysis (%) (for $C_7H_9N_2OS_2Cl$)

Calcd.: C, 35.51; H, 3.83; N, 11.83

Found : C, 35.33; H, 3.74; N, 11.68

In the same manner, the compound of Reference Example 15 was synthesized.

[Reference Example 17]

2-Methyl-5-pentylthio-4-oxazolecarbonitrile

According to the method of Matsumura et al. [Chem. Pharm. Bull., 21, 924, (1976)], 6.98 g of silver carbonate was permitted to act upon 2-acetylamino-3,3-bis(pentylthio)acrylonitrile to provide 1.25 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, J=7.2 Hz, 3H), 1.24-1.52 (m, 4H), 1.67 (qin, J=7.0 Hz, 2H), 2.50 (s, 3H), 2.99

(t, J=7.2 Hz, 2H).

Elemental analysis (%) (for $C_{10}H_{14}N_2OS$)

Calcd.: C, 57.11; H, 6.71; N, 13.32

Found : C, 56.98; H, 6.72; N, 13.34

In the same manner, the compounds of Reference Examples 18-21 and 23-26 were synthesized.

[Reference Example 27]

2-Methyl-5-phenethylthio-4-oxazolecarbonitrile

To a solution of phenethylmercaptan (0.98 g) in 20 ml of ethanol was added 0.41 g of sodium ethoxide and the mixture was stirred at room temperature for 15 minutes. The resulting solution was added gradually to a solution of 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile (1.0 g) in 20 ml of ethanol and the mixture was stirred at room temperature for 2.5 hours. The solvent was then distilled off and the residue was dissolved with ethyl acetate and washed with water to remove the salt. The organic layer was dried and concentrated to recover a yellow oil. This oil was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/10) to provide 1.13 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H), 2.99 (t, J=7.5 Hz, 2H), 3.25 (t, J=7.5 Hz, 2H), 7.15-7.35 (m, 5H).

Elemental analysis (%) (for $C_{13}H_{12}N_2OS$)

Calcd.: C, 63.91; H, 4.95; N, 11.47

Found : C, 63.89; H, 4.93; N, 11.44

In the same manner, the compounds of Reference Examples 30, 31, 53, 72, 85-103, 107, and 110 were synthesized.

[Reference Example 28]

2-Methyl-5-(3-phenylpropylthio)-4-oxazolecarbonitrile

To 0.93 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile synthesized in Example 1 was added 20 ml of methanol and the mixture was heated to provide a solution. To this solution was added 1.32 g of

sodium sulfide nonahydrate. Then, 1.0 g of 1-bromo-3-phenylpropane was added and the mixture was stirred at 50°C for 2 hours. Then, 100 ml of ethyl acetate was added and the mixture was washed with two 50 ml portions of water. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/3) to provide 0.72 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.96 (t, 2H), 2.47 (s, 3H), 2.77 (t, 2H), 2.96 (t, 2H), 7.15-7.32 (m, 5H).

Elemental analysis (%) (for $C_{14}H_{14}N_2OS$)

Calcd.: C, 65.09; H, 5.46; N, 10.84

Found : C, 65.12; H, 5.52; N, 10.74

In the same manner, the compounds of Reference Examples 29, 32-52, and 75-81 were synthesized.

[Reference Example 54]

5-Methylthio-2-trifluoromethyl-4-oxazolecarbonitrile

In 60 ml of N,N-dimethylformamide was dissolved 5.8 g of 3,3-dichloro-2-trifluoroacetylaminoacrylonitrile. Then, a solution of 12.5 g sodium sulfide nonahydrate in 8 ml water was added dropwise with ice-cooling and the mixture was stirred for 30 minutes. Then, 7.5 g of methyl iodide was added and the mixture was stirred with ice-cooling for another 30 minutes. This reaction mixture was diluted with 200 ml of water and extracted with two 200 ml portions of ethyl acetate. The combined ethyl acetate layer was washed with 100 ml of water, dried, and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1:3) to provide 4.98 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.75 (s, 3H)

Elemental analysis (%) (for $C_6H_3N_2OSF_3$)

Calcd.: C, 34.62; H, 1.45; N, 13.46

Found : C, 34.51; H, 1.44; N, 13.17

In the same manner, the compounds of Reference Examples 22 and 55-60 were synthesized.

[Reference Example 61]

5-Methylthio-2-phthalimidomethyl-4-oxazolecarbonitrile

To a solution of 2-chloromethyl-5-methylthio-4-oxazolecarbonitrile (0.20 g) in 20 ml of N,N-dimethylformamide was added a solution of potassium phthalimide (0.22 g) in 10 ml of N,N-dimethylformamide gradually and the mixture was stirred at room temperature for 2 hours. This reaction mixture was diluted with 100 ml of water and extracted with 3 portions of ethyl acetate. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 2/5) to provide 0.23 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.61 (s, 3H), 4.97 (s, 2H), 7.75-7.85 (m, 2H), 7.85-7.98 (m, 2H).

Elemental analysis (%) (for $C_{14}H_9N_3O_3S$)

Calcd.: C, 56.18; H, 3.03; N, 14.04

Found : C, 56.01; H, 3.02; N, 13.72

[Reference Example 62]

4-Hydroxymethyl-2-methyl-5-methylthiooxazole

In 25 ml of dry tetrahydrofuran was dissolved 2.00 g of the methyl 2-methyl-5-methylthio-4-oxazolecarboxylate synthesized in Reference Example 26, followed by addition of 0.34 g of lithium aluminum hydride in small portions under ice-cooling. The mixture was stirred under ice-cooling for 2 hours and, then, 0.34 ml of water, 0.34 ml of 15% aqueous sodium hydroxide solution, and 1 ml of water were successively added. The mixture was stirred for 30 minutes and filtered to remove insolubles. The filtrate was concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate) to

provide 0.73 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H), 2.46 (s, 3H), 3.25 (bs, 1H), 4.57 (d, J=4.2 Hz, 2H).

Elemental analysis (%) (for $C_6H_9NO_2S$)

Calcd.: C, 45.27; H, 5.70; N, 8.80

Found : C, 45.42; H, 5.61; N, 8.79

In the same manner, the compound of Reference Example 67 was synthesized.

[Reference Example 63]

2-Methyl-5-methylthio-4-oxazolylmethyl benzoate

In 10 ml of dichloromethane was dissolved 0.360 g of the 4-hydroxymethyl-2-methyl-5-methylthiooxazole synthesized in Reference Example 62 as well as 0.380 g of benzoyl chloride. To this solution under ice-cooling was added dropwise a solution of triethylamine (0.310 g) in dichloromethane (1 ml), and the mixture was stirred at room temperature overnight. To this reaction mixture was added an aqueous solution of sodium hydrogen carbonate and the mixture was extracted with two portions of dichloromethane. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1:2) to provide 0.533 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.40 (s, 3H), 2.48 (s, 3H), 5.27 (s, 2H), 7.42 (t, J=7.5 Hz, 2H), 7.55 (t, J=7.5 Hz, 1H), 8.07 (d, J=7.5 Hz, 2H).

Elemental analysis (%) (for $C_{13}H_{13}NO_3S$)

Calcd.: C, 59.30; H, 4.98; N, 5.32

Found : C, 59.23; H, 5.11; N, 5.28

[Reference Example 64]

(A) 4-(4-Chlorophenyloxymethyl)-2-methyl-5-methylthio-oxazole

(B) 4-(5-Chloro-2-hydroxyphenylmethyl)-2-methyl-5-methylthiooxazole

In 20 ml of dry tetrahydrofuran was dissolved

0.606 g of the 4-hydroxymethyl-2-methyl-5-methylthiooxazole synthesized in Reference Example 62 as well as 0.636 g of p-chlorophenol and 1.50 g of triphenylphosphine. Then, 0.995 g of diethyl azodicarboxylate was added dropwise under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and then, concentrated. The residue was chromatographed columnwise twice (silica gel; 1st run = ethyl acetate/n-hexane = 1/2, 2nd run = dichloromethane) to provide 0.213 g (oil) of title compound (A) and 0.449 g (solid) of title compound (B). (B) was recrystallized from dichloromethane/n-hexane.

(A) ^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H), 2.47 (s, 3H), 4.93 (s, 2H), 6.95 (d, J=6.8 Hz, 2H), 7.23 (d, J=6.8 Hz, 2H).

(B) ^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H), 2.43 (s, 3H), 3.80 (s, 2H), 6.89 (d, J=9.0 Hz, 1H), 7.10 (m, 2H), 9.66 (s, 1H).

Elemental analysis (%) (for $C_{12}H_{12}NO_2SCl$)

Calcd.: C, 53.43; H, 4.48; N, 5.19

Found : C, 53.01; H, 4.39; N, 4.94

[Reference Example 65]

4-Bromomethyl-2-methyl-5-methylthiooxazole

In 25 ml of dry tetrahydrofuran was dissolved 1.76 g of the 4-hydroxymethyl-2-methyl-5-methylthiooxazole synthesized in Reference Example 62 as well as 4.37 g of triphenylphosphine. After ice-cooling, 4.05 g of carbon tetrabromide was added and the mixture was stirred under ice-cooling for 1.5 hours. The insoluble matter was filtered off and the filtrate was concentrated. The residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1:2) to provide 1.95 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.39 (s, 3H), 2.46 (s, 3H), 4.41 (s, 2H).

[Reference Example 66]

Butyl 4-(2-methyl-5-methylthiooxazolyl) ketone

In a dry ice-ethanol bath, 2.1 ml of 1.6M n-butyllithium-n-hexane was added to a solution of 2-methyl-5-methylthio-4-oxazolecarbonitrile (1.0 g) in 10 ml of N,N-dimethylformamide under nitrogen atmosphere with stirring. The temperature was then increased to room temperature in 1.5 hours, after which the mixture was further stirred for 10 minutes. The solvent was then distilled off and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/9) to provide 0.23 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.93 (t, J=7.2 Hz, 3H), 1.38 (m, J=7.4 Hz, 2H), 1.67 (qin, J=7.4 Hz, 2H), 2.49 (s, 3H), 2.56 (s, 3H), 1.67 (t, J=7.5 Hz, 2H).

Elemental analysis (%) (for $C_{10}H_{15}NO_2S$)

Calcd.: C, 56.31; H, 7.09; N, 6.57

Found : C, 56.16; H, 7.04; N, 6.86

[Reference Example 68]

4-Chloromethyl-2-methyl-5-phenylthiooxazole

In 50 ml of chloroform was dissolved 3.02 g of the 4-hydroxymethyl-2-methyl-5-phenylthiooxazole synthesized in Reference Example 67. Under ice-cooling, 3.24 g of thionyl chloride was added dropwise and the mixture was stirred under ice-cooling for 0.5 hour. The reaction mixture was then concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) to provide 2.25 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 4.55 (s, 2H), 7.17-7.33 (m, 5H).

Elemental analysis (%) (for $C_{11}H_{10}NOSCl$)

Calcd.: C, 55.11; H, 4.20; N, 5.84

Found : C, 54.85; H, 4.12; N, 6.10

[Reference Example 69]

2-Methyl-5-phenylthio-4-oxazolylacetonitrile

In 7 ml of dimethyl sulfoxide was dissolved 1.00 g of the 4-chloromethyl-2-methyl-5-phenylthiooxazole synthesized in Reference Example 68, followed by addition of 0.31 g of sodium cyanide, and the mixture was stirred at room temperature overnight. The reaction mixture was poured in aqueous sodium chloride solution and extracted with 3 portions of ethyl acetate. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) to provide 0.656 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.48 (s, 3H), 3.68 (s, 2H), 7.19-7.34 (m, 5H).

Elemental analysis (%) (for $C_{12}H_{10}N_2OS$)

Calcd.: C, 62.59; H, 4.38; N, 12.16

Found : C, 62.32; H, 4.39; N, 11.93

[Reference Example 71]

N-isobutyl-(4-cyano-2-methyl-5-oxazolyl)thio-acetamide

In 16 ml of dichloromethane was dissolved 0.79 g of the (4-cyano-2-methyl-5-oxazolyl)thioglycolic acid synthesized in Reference Example 70 and, then under ice-cooling, 0.60 g of 1-hydroxybenzotriazole (HOBt), 0.84 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl), and 0.32 g of isobutylamine were added in that order. The mixture was stirred for 1 hour, after which it was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent: methanol/chloroform = 1/50) to provide 1.00 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.92 (d, 6H), 1.84 (m, 1H), 2.50 (s, 3H), 3.14 (t, 2H), 3.65 (s, 2H), 6.55 (broad, 1H).

Elemental analysis (%) (for $C_{11}H_{15}N_3O_2S$)

Calcd.: C, 52.15; H, 5.97; N, 16.59

Found : C, 50.34; H, 5.84; N, 15.77

In the same manner, the compound of Reference Example 74 was synthesized.

[Reference Example 82]

4-Cyano-5-methylthio-2-oxazolecarbohydrazide

In 30 ml of methanol was dissolved 1.49 g of the methyl 4-cyano-5-methylthio-2-oxazolecarboxylate synthesized as in Reference Example 54. To this solution was added 1.87 g of hydrazine hydrate at room temperature. The mixture was stirred at room temperature for 1 hour and the crystals that formed were harvested by filtration and dried to provide 0.77 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.74 (s, 3H), 4.09 (s, 2H), 8.11 (s, 1H).

Elemental analysis (%) (for $C_6H_6N_4O_2S$)

Calcd.: C, 36.36; H, 3.05; N, 28.27

Found : C, 36.28; H, 3.06; N, 28.32

[Reference Example 83]

4-Cyano-N'-formyl-5-methylthio-2-oxazolecarbohydrazide

In 15 ml of formic acid was dissolved 1.18 g of the 4-cyano-5-methylthio-2-oxazolecarbohydrazide synthesized in Reference Example 82 and the mixture was refluxed for 1 hour. This reaction mixture was concentrated to dryness under reduced pressure and 50 ml of methanol was added to the residue, whereupon crystals separated out. This crystal crop was harvested by filtration and dried to provide 0.53 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.75 (s, 3H), 8.12 (s, 1H), 10.2 (s, 1H), 11.1 (s, 1H).

Elemental analysis (%) (for $C_7H_6N_4O_3S$)

Calcd.: C, 37.17; H, 2.67; N, 24.77

Found : C, 37.09; H, 2.66; N, 24.79

[Reference Example 84]

5-Methylthio-2-(2-[1,3,4]-oxadiazolyl)-4-oxazole-

carbonitrile

To 1.12 g of the 4-cyano-N'-formyl-5-methylthio-2-oxazolecarbohydrazide synthesized in Reference Example 83 was added 250 ml of xylene and following addition of 0.7 g of phosphorus pentoxide, the mixture was refluxed for 3 hours with the dehydration by a Soxhlet's apparatus packed with molecular sieve 3A. The reaction mixture was distilled under reduced pressure. The ethyl acetate-soluble fraction was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) to provide 0.17 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.80 (s, 3H), 8.63 (s, 1H).

Elemental analysis (%) (for $C_7H_4N_4O_2S$)

Calcd.: C, 40.38; H, 1.94; N, 26.91

Found : C, 40.08; H, 1.98; N, 26.80

[Reference Example 105]

N-4-[5-(4-cyano-2-methyloxazolyl)thio]phenylmethanesulfonamide

In 10 ml of pyridine was dissolved 0.6 g of the 5-(4-aminophenylthio)-2-methyl-4-oxazolecarbonitrile synthesized in Reference Example 103, followed by addition of 0.39 g of methanesulfonyl chloride, and the mixture was stirred at room temperature for 7 hours. The pyridine was then distilled off under reduced pressure and the residue was dissolved in 50 ml of chloroform and washed with two 50 ml portions of water. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: chloroform/ethyl acetate = 10/1) and recrystallized from n-hexane-toluene to provide 0.62 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.48 (s, 3H), 3.06 (s, 3H), 6.83 (b, 1H), 7.20-7.28 (m, 2H), 7.50-7.56 (m, 2H).

Elemental analysis (%) (for $C_{12}H_{11}N_3O_3S_2$)

Calcd.: C, 46.59; H, 3.58; N, 13.58

Found : C, 46.65; H, 3.48; N, 13.55

In the same manner, the compound of Reference Example 106 was synthesized.

[Reference Example 111]

N-3-[5-(4-cyano-2-methyloxazolyl)thio]phenyl-N'-propylurea

In 20 ml of chloroform was dissolved 0.5 g of the 5-(3-aminophenylthio)-2-methyl-4-oxazolecarbonitrile synthesized in Reference Example 110 as well as 0.84 g of n-propyl isocyanate. To this solution was added 0.04 g of aluminum chloride and the mixture was stirred at room temperature for a day. This reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel; eluent: dichloromethane/n-hexane/ethyl acetate = 2/2/1) and recrystallized from toluene to provide 0.57 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.97 (t, 3H), 1.54-1.65 (m, 2H), 2.46 (s, 3H), 3.26 (dt, 2H), 5.12 (b, 1H), 6.96-7.68 (m, 4H), 8.29 (dd, 1H).

Elemental analysis (%) (for $C_{15}H_{16}N_4O_2S$)

Calcd.: C, 56.95; H, 5.10; N, 17.71

Found : C, 56.98; H, 5.06; N, 17.78

In the same manner, the compounds of Reference Examples 104, 108, and 109 were synthesized.

[Example 1]

2-Methyl-5-methylsulfonyl-4-oxazolecarbonitrile

To 400 ml of chloroform was added 10.0 g of 2-methyl-5-methylthio-4-oxazolecarbonitrile. Then, 28.0 g of m-chloroperbenzoic acid was added under ice-cooling and the mixture was stirred at room temperature for 2 hours and then, refluxed for 4 hours. This reaction mixture was washed with 2 portions of 10% aqueous sodium thiosulfate solution and 3 portions of saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the residue was washed with diethyl ether and dried in vacuo, whereby 9.8 g of

the title compound was obtained as crude crystals. A portion of this crude crystal crop was recrystallized from toluene to provide a pure product.

^{1}H-NMR ($CDCl_3$) δ: 2.65 (s, 3H), 3.30 (s, 3H).

Elemental analysis (%) (for $C_6H_6N_2O_3S$)

Calcd.: C, 38.71; H, 3.25; N, 15.05

Found : C, 39.16; H, 3.31; N, 14.59

In the same manner, the compounds of Examples 2-19, 21-55, 65, 75-78, 84-86, 99, 100, 116, 117, 119-121, 123, 125-128, 130, 142-146, 148-154, 157, 159, 160, 162, 164, 165, 167, 181-183, and 185-187 were synthesized.

[Example 20]

5-Methylsulfonyl-2-phenyl-4-oxazolecarboxamide

To a solution of 5-methylthio-2-phenyl-4-oxazolecarboxamide (0.13 g) in 5 ml of acetic acid was added a mixture of 30% hydrogen peroxide (0.23 g)-acetic acid (25 ml) and the whole mixture was stirred on an oil bath at 70°C for 7 hours. After 0.5% aqueous sodium thiosulfate solution was added, the reaction mixture was extracted with 200 ml of ethyl acetate and the extract was dried and concentrated. The residue was recrystallized from methanol to provide 0.10 g of the title compound.

^{1}H-NMR (DMSO-d_6) δ: 2.52 (s, 3H), 7.58-7.88 (m, 4H), 7.97 (bs, 2H), 8.06-8.18 (m, 2H).

Elemental analysis (%) (for $C_{11}H_{10}N_2O_4S$)

Calcd.: C, 49.62; H, 3.79; N, 10.52

Found : C, 49.48; H, 3.54; N, 10.65

[Example 56]

(A) 5-Methylsulfonyl-2-(4-nitrobenzyl)-4-oxazolecarbonitrile

(B) 5-Methylsulfonyl-2-(2-nitrobenzyl)-4-oxazolecarbonitrile

To a solution of sodium nitrate (0.39 g) in 6 ml of concentrated sulfuric acid was added 1.01 g of 2-

benzyl-5-methylsulfonyl-4-oxazolecarbonitrile portionwise with stirring and ice-cooling. After 1 hour of stirring under ice-cooling, the reaction mixture was diluted with 50 g of iced water and extracted with 3 portions of dichloromethane. The combined extract was dried and concentrated and the residue was fractionated and purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane/dichloromethane = 1/1/1). The fractions were respectively recrystallized from dichloromethane/n-hexane (1:1) to provide 0.84 g of the title compound (A) and 0.37 g of the title compound (B).

(A) ^{1}H-NMR ($CDCl_3$) δ: 3.29 (s, 3H), 4.35 (s, 2H), 7.53 (d, J=8.7 Hz, 2H), 8.26 (d, J=8.7 Hz, 2H).

Elemental analysis (%) (for $C_{12}H_9N_3O_5S$)

Calcd.: C, 46.90; H, 2.95; N, 13.67

Found : C, 46.35; H, 2.89; N, 13.39

(B) ^{1}H-NMR ($CDCl_3$) δ: 3.31 (s, 3H), 4.59 (s, 2H), 7.45-7.80 (m, 3H), 8.15-8.30 (m, 1H).

Elemental analysis (%) (for $C_{12}H_9N_3O_5S$)

Calcd.: C, 46.90; H, 2.95; N, 13.67

Found : C, 46.48; H, 3.10; N, 13.43

[Example 58]

2-Bromo-5-methylsulfonyl-4-oxazolecarbonitrile

In a dry ice-ethanol bath, 1.2 ml of 1.6M n-butyllithium-n-hexane was added to a solution of 5-methylsulfonyl-4-oxazolecarbonitrile (0.30 g) in 30 ml of tetrahydrofuran under nitrogen atmosphere and the mixture was stirred for 30 minutes. Then, 0.31 g of bromine was added dropwise and the mixture was further stirred under the same conditions for 30 minutes. The reaction was then stopped by adding 10% aqueous sodium thiosulfate solution and the mixture was extracted with 3 portions of ethyl acetate. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: chloroform)

to provide 0.07 g of the title compound.
^{1}H-NMR ($CDCl_3$) δ: 3.34 (s, 3H).
Elemental analysis (%) (for $C_5H_3N_2O_3SBr$)
Calcd.: C, 23.92; H, 1.20; N, 11.16
Found : C, 24.00; H, 1.15; N, 11.05

[Example 59]

2-Methylamino-5-methylsulfonyl-4-oxazolecarbonitrile

To a solution of 2-bromo-5-methylsulfonyl-4-oxazolecarbonitrile (1.0 g) in 80 ml of dichloromethane was added a mixture of 40% methylamine-methanol (0.33 g) and triethylamine (0.42 g) dropwise under ice-cooling and the mixture was then stirred at room temperature for 2 hours. The solvent was then distilled off and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane/dichloromethane = 1/1/1) to provide 0.68 g of the title compound.
^{1}H-NMR ($CDCl_3$) δ: 3.10 (d, J=5.1 Hz, 3H), 3.23 (s, 3H), 5.22 (bs, 1H).
Elemental analysis (%) (for $C_6H_7N_3O_3S$)
Calcd.: C, 35.82; H, 3.51; N, 20.88
Found : C, 35.57; H, 3.53; N, 20.68

In the same manner, the compounds of Examples 60 and 61 were synthesized.

[Example 62]

2-(N-benzyl-N-methylaminomethyl)-5-methylsulfonyl-4-oxazolecarbonitrile

To a solution of 2-chloromethyl-5-methylsulfonyl-4-oxazolecarbonitrile (0.23 g) in 60 ml of dichloromethane was added a solution of benzylmethylamine (0.15 g) and triethylamine (0.13 g) in 20 ml of dichloromethane gradually under ice-cooling and the mixture was refluxed overnight. The solvent was then distilled off and the yellow residue was purified by column chromatography (silica gel; eluent:

ethyl acetate/n-hexane/dichloromethane = 1/1/1) to provide 0.03 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H), 3.29 (s, 3H), 3.67 (s, 2H), 3.83 (s, 2H), 7.25-7.40 (m, 5H).

Elemental analysis (%) (for $C_{14}H_{15}N_3O_3S$)

Calcd.: C, 55.07; H, 4.95; N, 13.76

Found : C, 55.26; H, 4.96; N, 13.50

In the same manner, the compounds of Examples 131-133 were synthesized.

[Example 63]

5-Methylsulfonyl-2-(4-phenyl-1-piperazinylmethyl)-4-oxazolecarbonitrile

To a solution of 2-chloromethyl-5-methylsulfonyl-4-oxazolecarbonitrile (0.30 g) in 50 ml of acetonitrile were added 0.05 g of potassium iodide, 0.23 g of phenylpiperazine, and 0.20 g of potassium carbonate and the mixture was stirred at room temperature for 30 minutes. This reaction mixture was filtered and the solvent was distilled off. The yellow residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane/dichloromethane = 1/1/1) and recrystallized from dichloromethane/n-hexane (1:1) to provide 0.48 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.78 (t, J=4.9 Hz, 4H), 3.24 (t, J=5.0 Hz, 4H), 3.33 (s, 3H), 3.89 (s, 2H), 6.83-7.00 (m, 3H), 7.22-7.33 (m, 2H).

Elemental analysis (%) (for $C_{16}H_{18}N_4O_3S$)

Calcd.: C, 55.48; H, 5.24; N, 16.17

Found : C, 55.27; H, 5.25; N, 16.14

[Example 64]

(A) 2-(4-Methylphenylsulfonylmethyl)-5-methylsulfonyl-4-oxazolecarbonitrile

(B) 5-(4-Methylphenylsulfonyl)-2-(4-methylphenylsulfonylmethyl)-4-oxazolecarbonitrile

To a solution of 2-chloromethyl-5-methylsulfonyl-4-oxazolecarbonitrile (0.16 g) in 30 ml of N,N-

dimethylformamide was added 0.19 g of sodium p-toluenesulfinate with ice-cooling and the mixture was stirred at room temperature for 20 minutes. This reaction mixture was diluted with 100 ml of water and extracted with 3 portions of ethyl acetate. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from dichloromethane/n-hexane to provide 0.12 g of the title compound (A) and 0.03 g of the title compound (B).

(A) ^{1}H-NMR ($CDCl_3$) δ: 2.50 (s, 3H), 3.30 (s, 3H), 4.64 (s, 2H), 7.42 (d, J=8.6 Hz, 2H), 7.72 (d, J=8.6 Hz, 2H).

Elemental analysis (%) (for $C_{13}H_{12}N_2O_5S$)

Calcd.: C, 45.87; H, 3.55; N, 8.23

Found : C, 45.69; H, 3.56; N, 8.29

(B) ^{1}H-NMR ($CDCl_3$) δ: 2.48 (s, 3H), 2.50 (s, 3H), 4.54 (s, 2H), 7.32 (d, J=8.6 Hz, 2H), 7.46 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.95 (d, J=8.6 Hz, 2H).

Elemental analysis (%) (for $C_{19}H_{16}N_2O_5S_2$)

Calcd.: C, 54.79; H, 3.87; N, 6.78

Found : C, 54.28; H, 3.84; N, 6.68

[Example 66]

2-Methyl-5-methylsulfonyl-4-oxazolecarboxamide

To 3 ml of concentrated sulfuric acid was added 1.0 g of 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile portionwise with ice-cooling and the mixture was stirred at room temperature for 3 hours. To this reaction mixture was added 20 ml of iced water and the precipitate that formed was recovered by filtration, rinsed with a small amount of cold water, and dried in vacuo. This crystal crop was recrystallized from methanol to provide 0.49 g of the title compound.

^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H), 3.56 (s, 3H), 7.92 (bs, 1H), 8.02 (bs, 1H).

Elemental analysis (%) (for $C_6H_8N_2O_4S$)

Calcd.: C, 35.29; H, 3.95; N, 13.72

Found : C, 35.30; H, 3.75; N, 13.75

In the same manner, the compound of Example 67 was synthesized.

[Example 68]

2-Methyl-5-methylsulfonyl-4-oxazolecarboxylic acid

To 3.44 g of the methyl 2-methyl-5-methylsulfonyl-4-oxazolecarboxylate synthesized in Example 19 was added 4.61 g of 15% sodium hydroxide and 30 ml of water and the mixture was stirred at room temperature for 1 hour. This reaction mixture was made acidic with diluted sulfuric acid and extracted with 10 portions of ethyl acetate. The combined extract was dried and concentrated and the residue was recrystallized from methanol-diethyl ether-hexane to provide 2.66 g of the title compound.

^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H), 3.50 (s, 3H).

Elemental analysis (%) (for $C_6H_7NO_5S$)

Calcd.: C, 35.12; H, 3.44; N, 6.83

Found : C, 35.16; H, 3.44; N, 6.90

In the same manner, the compounds of Example 98 and Reference Examples 70 and 73 were respectively synthesized.

[Example 69]

N-benzyl-2-methyl-5-methylsulfonyl-4-oxazole-carboxamide

To 1.00 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarboxylic acid synthesized in Example 68 was added 10 ml of thionyl chloride and the mixture was refluxed for 6 hours. The thionyl chloride was then distilled off and the solid residue was dissolved in 15 ml of dichloromethane. Then, a solution of benzylamine (0.57 g) and triethylamine (0.54 g) in dichloromethane

(1 ml) was added dropwise with ice-cooling. After 1 hour of stirring under ice-cooling, the reaction mixture was poured in water and extracted with 3 portions of dichloromethane. The combined extract was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate) and recrystallized from ethanol to provide 1.36 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (s, 3H), 3.56 (s, 3H), 4.61 (d, J=6.0 Hz, 2H), 7.34 (m, bs, 6H).

Elemental analysis (%) (for $C_{13}H_{14}N_2O_4S$)

Calcd.: C, 53.05; H, 4.79; N, 9.52

Found : C, 52.97; H, 4.80; N, 9.59

In the same manner, the compounds of Examples 70-74 were synthesized.

[Example 79]

4-(N-benzyl-N-methylaminomethyl)-2-methyl-5-methylsulfonyloxazole

In 15 ml of dichloromethane was dissolved 0.350 g of the 4-bromomethyl-2-methyl-5-methylsulfonyloxazole synthesized in Example 78. To this solution was added a solution of N-methylbenzylamine (0.217 g) and triethylamine (0.182 g) in dichloromethane (1 ml) dropwise under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and at room temperature for another hour, after which it was concentrated. The residue was purified by column chromatography (silica gel; eluent: ethyl acetate) to provide 0.322 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (s, 3H), 2.68 (s, 3H), 3.17 (s, 3H), 3.64 (s, 2H), 3.78 (s, 2H), 7.20-7.38 (m, 5H).

In the same manner, the compounds of Examples 80 and 81 were synthesized.

[Example 83]

2-Methyl-4-(4-methylphenylsulfonylmethyl)-5-

methylsulfonyloxazole

In 5 ml of N,N-dimethylformamide was dissolved 0.250 g of the 4-bromomethyl-2-methyl-5-methylsulfonyloxazole synthesized in Example 78, followed by addition of 0.258 g of sodium p-toluenesulfinate tetrahydrate under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and then, concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent: ethyl acetate) and recrystallized from dichloromethane/diethyl ether/n-hexane to provide 0.231 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 2.58 (s, 3H), 3.30 (s, 3H), 4.62 (s, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.82 (d, J=8.4 Hz, 2H).

Elemental analysis (%) (for $C_{13}H_{15}NO_5S_2$)

Calcd.: C, 47.40; H, 4.59; N, 4.25

Found : C, 47.16; H, 4.47; N, 4.37

In the same manner, the compound of Example 82 was synthesized.

[Example 87]

2-Methyl-5-phenylsulfonyl-4-oxazolylacetic acid

To 10 ml of concentrated sulfuric acid was added 0.200 g of the 2-methyl-5-phenylsulfonyl-4-oxazolyl-acetonitrile synthesized in Example 86 and the mixture was heated at 115°C for 2 hours. This reaction mixture was added in small portions to iced water and extracted with 2 portions of ethyl acetate. The combined extract was washed with aqueous sodium chloride solution once, dried, and concentrated. The residue was recrystallized from dichloromethane/n-hexane to provide 0.151 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 4.06 (s, 2H), 6.80 (b, 1H), 7.50-7.72 (m, 3H), 7.96-8.05 (m, 2H).

Elemental analysis (%) (for $C_{12}H_{11}NO_5S$)

Calcd.: C, 51.24; H, 3.94; N, 4.98

Found : C, 50.84; H, 3.88; N, 4.79

[Example 88]

2-Methyl-5-methylsulfonyl-4-oxazolecarbothioamide

To 80 ml of dry tetrahydrofuran was added 2.00 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarboxamide synthesized in Example 66 as well as 2.77 g of Lawesson's reagent and the mixture was refluxed for 6 hours. This reaction mixture was concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/1) and recrystallized from ethyl acetate to provide 0.60 g of the title compound.

^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 3H), 3.49 (s, 3H), 9.78 (bs, 1H), 10.31 (bs, 1H).

Elemental analysis (%) (for $C_6H_8N_2O_3S_2$)

Calcd.: C, 32.72; H, 3.66; N, 12.72; S, 29.11

Found : C, 32.83; H, 3.55; N, 12.52; S, 28.75

In the same manner, the compounds of Examples 89-92 were synthesized.

[Example 93]

2-Methyl-5-pentylsulfonyl-4-oxazolecarbothioamide

In 6.6 ml of tetrahydrofuran/water (10:1) was dissolved 0.170 g of the 2-methyl-5-pentylsulfonyl-4-oxazolecarboxamide synthesized in Example 4, followed by addition of 0.390 g of O,O'-diethyl dithiophosphate, and the mixture was refluxed for 9 hours. This reaction mixture was concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/1) to provide 0.108 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, J=7.0 Hz, 3H), 1.25-1.50 (m, 4H), 1.70-1.90 (m, 2H), 2.60 (s, 3H), 3.56-3.67 (m, 2H), 7.70 (bs, 1H), 8.60 (bs, 1H).

MS m/z 276 (M^+)

In the same manner, the compounds of Examples 94, 95, and 135-139 were synthesized.

[Example 96]

2-Methyl-5-methylsulfonyl-4-(4-phenylthiazolyl)-oxazole

In 20 ml of ethanol was dissolved 0.150 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarbothioamide synthesized in Example 88 as well as 0.162 g of phenacyl bromide and the solution was refluxed for 1 hour. This reaction mixture was concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from dichloromethane/n-hexane to provide 0.112 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.64 (s, 3H), 3.67 (s, 3H), 7.33-7.54 (m, 3H), 7.67 (s, 1H), 7.89-8.00 (m, 2H).

Elemental analysis (%) (for $C_{14}H_{12}N_2O_3S_2$)

Calcd.: C, 52.48; H, 3.78; N, 8.74

Found : C, 52.18; H, 3.92; N, 8.82

In the same manner, the compound of Example 97 was synthesized.

[Example 101]

(E)-5-(2-N,N-dimethylaminoethenylsulfonyl)-2-methyl-4-oxazolecarbonitrile

To a solution of 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile (1.0 g) in 10 ml of N,N-dimethylformamide was added 0.83 g of N,N-dimethylformamide dimethyl acetal and the mixture was stirred at room temperature for 4 hours and further on an oil bath at 50°C for 15 minutes. The solvent was then distilled off and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 4/5) to provide 0.64 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (s, 3H), 2.88 (s, 3H), 3.18 (s, 3H), 4.97 (d, J=12 Hz, 1H), 7.44 (d, J=12 Hz, 1H).

Elemental analysis (%) (for $C_9H_{11}N_3O_3S$)

Calcd.: C, 44.80; H, 4.60; N, 17.42

Found : C, 44.63; H, 4.44; N, 17.24

[Example 102]

2-Methyl-5-(2-methyl-4-cyano-5-oxazolyl)methylsulfonyl-4-oxazolecarbonitrile

In 20 ml of N,N-dimethylformamide was dissolved 0.93 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile synthesized in Example 1, followed by addition of 0.24 g of sodium hydride (ca. 60%) under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and then at room temperature for another hour. This reaction mixture was diluted with 100 ml of ethyl acetate and washed with 50 ml of water twice. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from ethyl acetate/n-hexane to provide 0.12 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.58 (s, 3H), 2.69 (s, 3H), 4.77 (s, 2H).

Elemental analysis (%) (for $C_{11}H_8N_4O_4S$)

Calcd.: C, 45.21; H, 2.76; N, 19.17

Found : C, 45.17; H, 2.76; N, 19.20

In the same manner, the compound of Example 188 was synthesized.

[Example 104]

2-Methyl-5-[2-(4-methylsulfonamidophenyl)ethylsulfonyl]-4-oxazolecarbonitrile

In 5 ml of pyridine was dissolved 0.25 g of the 2-methyl-5-[2-(4-aminophenyl)ethylsulfonyl]-4-oxazolecarbonitrile synthesized in Example 103, followed by addition of 0.12 g of methanesulfonyl chloride, and the mixture was stirred at room temperature for 1 hour. This reaction mixture was diluted with 50 ml of ethyl acetate and washed with two 50 ml portions of water. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica

gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from methanol to provide 0.20 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.56 (s, 3H), 3.05 (s, 3H), 3.20 (t, 2H), 3.65 (t, 2H), 6.04 (s, 1H), 7.16 (s, 2H).

Elemental analysis (%) (for $C_{14}H_{15}N_3O_5S_2$)

Calcd.: C, 45.52; H, 4.09; N, 11.37

Found : C, 45.44; H, 4.07; N, 11.24

In the same manner, the compounds of Examples 105 and 106 were synthesized.

[Example 107]

5-(4-Aminophenylsulfonyl)-2-methyl-4-oxazolecarbonitrile

In 10 ml of tetrahydrofuran was dissolved 0.20 g of the 2-methyl-5-(4-nitrophenylsulfonyl)-4-oxazolecarbonitrile synthesized in Example 40. Then, 1.3 ml of concentrated hydrochloric acid and 0.15 g of iron powder were added under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and then, neutralized with saturated aqueous $NaHCO_3$ solution. The mixture was concentrated and the residue was diluted with 100 ml of ethyl acetate and washed with 15% aqueous NaOH solution. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: n-hexane/dichloromethane/ethyl acetate = 2/2/1) and recrystallized from n-hexane/toluene to provide 0.044 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.53 (s, 3H), 4.20 (b, 2H), 6.71-6.76 (m, 2H), 7.80-7.85 (m, 2H).

In the same manner, the compounds of Examples 57 and 103 were synthesized.

[Example 108]

N-isobutyl-4-cyano-2-methyl-5-oxazolesulfonamide

In 20 ml of hot methanol was dissolved 1.00 g of the 2-methyl-5-methylsulfonyl-4-oxazolecarbonitrile

synthesized in Example 1, followed by addition of 1.40 g of sodium sulfide nonahydrate. The mixture was stirred at room temperature for 1 hour and acidified to below pH=3 with 1N-HCl. This reaction mixture was concentrated to dryness under reduced pressure and 6 ml of acetonitrile was added. The insoluble matter was filtered off and the filtrate was cooled to -10°C. Then, 1.35 g of potassium nitrate and 1.81 g of thionyl chloride were added. The mixture was filtered to remove the insoluble matter. To the filtrate was added 40 ml of pyridine, followed by addition of 0.46 g of isobutylamine, and the mixture was stirred at room temperature for 1 hour. This reaction mixture was diluted with 200 ml of ethyl acetate and washed with two 100 ml portions of water. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/3) and recrystallized from ethyl acetate/n-hexane to provide 0.095 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (d, 6H), 1.84 (m, 1H), 2.60 (s, 3H), 3.05 (t, 2H), 5.28 (t, 1H).

Elemental analysis (%) (for $C_9H_{13}N_3O_3S$)

Calcd.: C, 44.43; H, 5.39; N, 17.27

Found : C, 44.15; H, 5.17; N, 17.15

In the same manner, the compounds of Examples 109-112 and 189-205 were synthesized.

[Example 113]

4-Bromomethyl-2-methyl-5-methylsulfinyloxazole

In 30 ml of dichloromethane was dissolved 3.55 g of the 4-bromomethyl-2-methyl-5-methylthiooxazole synthesized in Reference Example 65, followed by addition of 2.76 g of m-chloroperbenzoic acid with ice-cooling. The mixture was stirred at room temperature for 1 hour and then washed with 10% aqueous sodium thiosulfate solution once and 2 portions of saturated

aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate) and recrystallized from dichloromethane/hexane to provide 1.10 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 2.57 (s, 3H), 3.01 (s, 3H), 4.47 (s, 2H).

Elemental analysis (%) (for $C_6H_8NO_2SBr$)

Calcd.: C, 30.27; H, 3.39; N, 5.88

Found : C, 30.01; H, 3.46; N, 5.86

In the same manner, the compounds of Examples 114, 115, 118, 122, 124, 129, 147, 155, 156, 158, 161, 163, 166 and 184 were synthesized.

[Example 134]

(A) 5-Methylsulfinyl-2-(2-[1,3,4]-oxadiazolyl)-4-oxazolecarbonitrile

(B) 5-Methylsulfonyl-2-(2-[1,3,4]-oxadiazolyl)-4-oxazolecarbonitrile

In chloroform was dissolved 0.90 g of the 5-methylthio-2-(2-[1,3,4]-oxadiazolyl)-4-oxazolecarbonitrile synthesized in Reference Example 84, followed by addition of 0.90 g of m-chloroperbenzoic acid with cooling. The reaction was carried out at room temperature for 2 hours, after which the reaction mixture was washed with 2 portions of saturated aqueous $NaHCO_3$ solution. The chloroform layer was dried and concentrated and the residue was fractionated and purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) to provide 0.25 g of the title compound (A) and 0.057 g of the title compound (B).

(A) ^{1}H-NMR ($CDCl_3$) δ: 3.24 (s, 3H), 8.71 (s, 1H).

Elemental analysis (%) (for $C_7H_4N_4O_3S$)

Calcd.: C, 37.50; H, 1.80; N, 24.99

Found : C, 37.20; H, 1.94; N, 24.49

(B) ^{1}H-NMR ($CDCl_3$) δ: 3.43 (s, 3H), 8.73 (s, 1H).

Elemental analysis (%) (for $C_7H_4N_4O_4S$)

Calcd.: C, 35.00; H, 1.68; N, 23.33

Found : C, 35.42; H, 1.73; N, 23.34

[Example 140]

2-Methyl-5-phenylsulfonyl-4-oxazolecarboxylic acid

The title compound was synthesized in the same manner as in Example 68 and the resulting oil was crystallized from methanol.

^{1}H-NMR ($CDCl_3$)δ: 2.59 (s, 3H), 7.76-7.90 (m, 3H), 8.14 (m, 2H).

Elemental analysis (%) (for $C_{11}H_9NO_5S \cdot CH_3OH$)

Calcd.: C, 48.15; H, 4.38; N, 4.68

Found : C, 47.76; H, 4.13; N, 4.77

[Example 141]

t-Butyl 4-(2-Methyl-5-phenylsulfonyloxazolyl)-carbamate

To 15 ml of t-butyl alcohol was added 0.65 g of the 2-methyl-5-phenylsulfonyl-4-oxazolecarboxylic acid synthesized in Example 140, followed by addition of 0.23 g of diphenylphosphorylazide (DPPA) and 0.09 g of triethylamine, and the mixture was refluxed for 2 hours. The solvent was then distilled off and the residue was dissolved in 30 ml of dichloromethane. This solution was washed with 5% aqueous citric acid solution and saturated aqueous $NaHCO_3$ solution in the order mentioned. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/1) and recrystallized from dichloromethane/n-hexane to provide the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.55 (s, 9H), 2.48 (s, 3H), 7.53-7.67 (m, 3H), 7.84 (bs, 1H), 7.93-8.00 (m, 2H).

Elemental analysis (%) (for $C_{15}H_{18}N_2O_5S$)

Calcd.: C, 53.24; H, 5.36; N, 8.28

Found : C, 53.18; H, 5.34; N, 8.29

[Example 168]

2-(2-Methoxybenzyl)-5-methylsulfonyl-4-oxazole-carbonitrile

To 1.86 g of 2-methoxyphenylacetic acid was added 8 ml of thionyl chloride and the mixture was refluxed for 1 hour. The thionyl chloride was distilled off and the residual oil was dissolved in 50 ml of ethyl acetate. To this solution was added 1.50 g of 2-amino-3,3-dichloroacrylonitrile and the mixture was stirred at room temperature for 17 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was recrystallized from diethyl ether/n-hexane to give 1.57 g of needles. Then, as in Reference Example 54, this crystal crop was dissolved in 50 ml of N,N-dimethylformamide and with ice-cooling, a solution of sodium sulfide nonahydrate (2.76 g) in water (5 ml) was added dropwise. The mixture was stirred for 5 minutes, after which 1.60 g of methyl iodide was added and the mixture was further stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced pressure and the residue was diluted with 100 ml of ethyl acetate and 50 ml of water. The ethyl acetate layer was taken, washed with two 50 ml portions of water, dried, and concentrated. Then, as in Example 1, the oily residue was dissolved in 100 ml of chloroform, and after addition of 3.80 g of m-chloroperbenzoic acid under ice-cooling, the mixture was refluxed for 4 hours. This reaction mixture was washed with 2 portions of 10% aqueous sodium thiosulfate solution twice and 3 portions of saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the residue was purified by column chromatography (silica gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from ethyl acetate/n-hexane (1:1) to provide 0.53 g of the title compound. ^{1}H-NMR ($CDCl_3$) δ: 3.26 (s, 3H), 3.81 (s, 3H), 4.21 (s,

2H), 6.80-7.40 (m, 4H).

Elemental analysis (%) (for $C_{13}H_{12}N_2O_4S$)

Calcd.: C, 53.42; H, 4.14; N, 9.58

Found : C, 53.41; H, 4.11; N, 9.65

In the same manner, the compounds of Example 169-178 were synthesized.

[Example 179]

2-(3-Methoxybenzyl)-5-methylsulfonyl-4-oxazole-carbonitrile

In 50 ml of ethyl acetate was dissolved 0.7 g of 2-amino-3,3-dichloroacrylonitrile, followed by addition of 0.98 g of 3-methoxyphenylacetyl chloride, and the mixture was stirred at room temperature for 17 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was recrystallized from diethyl ether/n-hexane (1:3) to provide 1.1 g of needles. As in Reference Example 54, this crystal crop was dissolved in 50 ml of N,N-dimethylformamide, and under ice-cooling, a solution of sodium sulfide nonahydrate (1.95 g) in water (5 ml) was added dropwise. The mixture was stirred for 5 minutes, after which 1.2 g of methyl iodide was added and the mixture was further stirred at room temperature for 4 hours. This reaction mixture was concentrated under reduced pressure and the residue was diluted with 50 ml of water and extracted with 100 ml of ethyl acetate. The ethyl acetate layer was washed with two 50 ml portions of water, dried, and concentrated. As in Example 1, the oil thus obtained was dissolved in 100 ml of chloroform, and under ice-cooling, 2.34 g of m-chloroperbenzoic acid was added. The mixture was then refluxed for 4 hours. This reaction mixture was washed with 2 portions of 10% aqueous sodium thiosulfate solution and 3 portions of saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated and the residue was purified by column chromatography

(silica gel; eluent: ethyl acetate/n-hexane = 1/2) and recrystallized from ethyl acetate/n-hexane (1:2) to provide 0.12 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 3.27 (s, 3H), 3.82 (s, 3H), 4.18 (s, 2H), 6.80-6.95 (m, 3H), 7.20-7.40 (m, 1H).

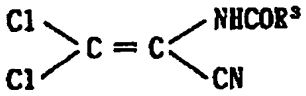
Elemental analysis (%) (for $C_{13}H_{12}N_2O_4S$)

Calcd.: C, 53.42; H, 4.14; N, 9.58

Found : C, 53.56; H, 4.13; N, 9.47

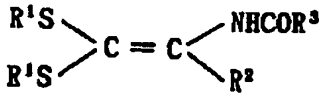
In the same manner, the compound of Example 180 was synthesized.

[Table 4] Compounds of Reference Examples



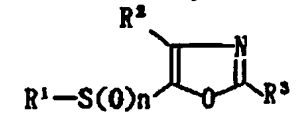
Ref. Ex. No.	R^3	m. p. (℃)	IR Spectrum (cm^{-1})
1	$n\text{-}C_5H_{11}$	76.5-79	3250. 2230. 1680. 1490. 1290
2	Ph	136.5-137.5	3250. 2240. 1660. 1600. 1480. 1290
3	CH_2Ph	167-168.5	3240. 2230. 1670. 1490. 1280. 1180. 900
4	$(CH_2)_2Ph$	118-121	3260. 2230. 1680. 1600. 1495
5	CF_2CF_3	118-119	3260. 2230. 1730. 1600. 1510. 1350. 1200. 1160
6	OCH_3	112-113	3250. 2230. 1710. 1600. 1510. 1290
7	$NHCH_2CO_2C_4H_9(n)$	130-131	3310. 2240. 1730. 1650

[Table 5] Compounds of Reference Examples



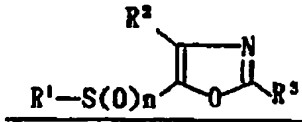
Ref. Ex. No.	R^1	R^2	R^3	m. p. (℃)	IR Spectrum(cm^{-1})
8	n-C_5H_{11}	CN	CH_3	oil	3270, 2220, 1670, 1560, 1470, 1280
9	n-$C_{10}H_{21}$	CN	CH_3	42-43.5	3270, 2220, 1670, 1560, 1470, 1280
10	CH_2Ph	CN	CH_3	140-141.5	3270, 2220, 1670, 1560, 1490, 1280
11	CH_3	CN	n-C_5H_{11}	82.5-84.5	3250, 2210, 1660, 1560, 1490
12	CH_3	CN	Ph	115.5-117	3260, 2210, 1660, 1480, 1290
13	CH_3	CN	$(CH_2)_2Ph$	111.5-115	3280, 2210, 1670, 1560, 1490, 1260
14	CH_3	CN	CH_2Cl	111-112	3270, 2210, 1670, 1560, 1500
15	CH_3	CN	$(CH_2)_2CO_2CH_3$	123.5-128	3450, 3220, 2210, 1740, 1670, 1420, 1170
16	CH_3	CO_2CH_3	CH_3	81-82.5	3320, 3230, 1740, 1710, 1690, 1580

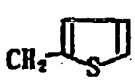
[Table 6] Compounds of Reference Examples and Examples



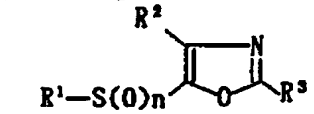
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
CH_3	CN	CH_3	2	Ex. 1	106.5-107.5	2250, 1580, 1340, 1150
C_2H_5	CN	CH_3	2	Ex. 2	65.5-68	2250, 1580, 1340, 1300, 1150
n-C_4H_9	CN	CH_3	2	EX. 3	65-66	2250, 1570, 1350, 1300, 1150
n-C_5H_{11}	CN	CH_3	0	Ref. Ex. 17	oil	2240, 1580, 1120
			2	Ex. 4	67.5-70	2250, 1580, 1340, 1300, 1150
n-$C_{10}H_{21}$	CN	CH_3	0	Ref. Ex. 18	oil	2240, 1580, 1120
			2	Ex. 5	81.5-82.5	2250, 1570, 1340, 1300, 1150
Ph	CN	CH_3	2	Ex. 6	119-120.5	2250, 1580, 1350, 1160
CH_2Ph	CN	CH_3	0	Ref. Ex. 19	oil	2240, 1580, 1460, 1120
			2	Ex. 7	152-153.5	2250, 1570, 1350, 1300, 1150, 1130
CH_3	CN	H	2	Ex. 8	94.5-96.5	2260, 1490, 1340, 1150, 1080, 960
CH_3	CN	C_2H_5	2	Ex. 9	92-93	2250, 1560, 1320, 1140
CH_3	CN	n-C_3H_7	2	Ex. 10	73-73.5	2250, 1560, 1330, 1140, 970
CH_3	CN	n-C_5H_{11}	0	Ref. Ex. 20	oil	2240, 1580, 1130, 1080
			2	Ex. 11	63-64	2250, 1570, 1330, 1140, 970, 780
CH_3	CN	Ph	0	Ref. Ex. 21	oil	2230, 1560, 1530, 1160, 1090
			2	Ex. 12	205-206.5	2230, 1550, 1340, 1150, 960

[Table 7]



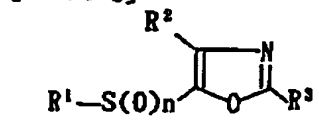
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spctrum(cm^{-1})
CH_3	CN	CH_2Ph	0	Ref. Ex. 22	oil	2240. 1580. 1500. 1120. 740
			2	Ex. 13	102-103.5	2250. 1560. 1330. 1160. 990
CH_3	CN	$(CH_2)_2Ph$	0	Ref. Ex. 23	oil	2240. 1580. 1130
			2	Ex. 14	73.5-74.5	2250. 1570. 1350. 1160. 960. 770
CH_3	CN	CH_2Cl	0	Ref. Ex. 24	oil	2240. 1530. 1430. 1130. 1080. 780
			2	Ex. 15	98-99.5	2260. 1580. 1350. 1160. 980
CH_3	CN	$(CH_2)_2CO_2CH_3$	0	Ref. Ex. 25	oil	2240. 1740. 1580. 1440. 1210
			2	Ex. 16	96-97	2250. 1740. 1570. 1340. 1150
Ph	CN	C_2H_5	2	Ex. 17	92-93	2250. 1560. 1320. 1140
Ph	CN	n-C_3H_7	2	Ex. 18	81-82	2250. 1560. 1450. 1350. 1150
CH_3	CO_2CH_3	CH_3	0	Ref. Ex. 26	84-85	1710. 1600. 1520
			2	Ex. 19	122-124	1730. 1580. 1330. 1130
Ph	$CONH_2$	CH_3	2	Ex. 20	169-171	3410. 3300. 1710. 1680. 1330. 1150
CH_3	$CONHCOCH_3$	CH_3	2	Ex. 21	155.5-157	3440. 3250. 1750. 1690. 1340. 1170
$(CH_2)_2Ph$	CN	CH_3	0	Ref. Ex. 27	oil	2240. 1580. 1120
			2	Ex. 22	83.5-85.5	2250. 1570. 1350. 1330. 1150
$(CH_2)_3Ph$	CN	CH_3	0	Ref. Ex. 28	oil	3030. 2930. 2240. 1580. 1530. 1500. 1440. 1380. 1300. 1260. 1120
			2	Ex. 23	82.5-84.0	3030. 2940. 2250. 1570. 1500. 1460. 1380. 1310. 1250. 1180. 1150
	CN	CH_3	0	Ref. Ex. 29	oil	2240. 1580. 1260. 1120. 710
			2	Ex. 24	120-121.5	2250. 1570. 1340. 1300. 1150

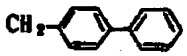
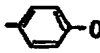
[Table 8]



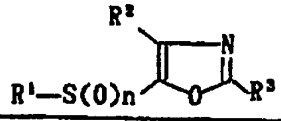
R^1	R^2	R^3	n	No.	m.p. (T)	IR Spectrum(cm^{-1})
$CH_2CO_2C_2H_5$	CN	CH_3	0	Ref. Ex. 30	oil	2240, 1740, 1580, 1300, 1130
			2	Ex. 25	89.5-90.5	2250, 1750, 1570, 1350, 1300, 1140
$(CH_2)_2CO_2C_2H_5$	CN	CH_3	0	Ref. Ex. 31	oil	2240, 1740, 1580
			2	Ex. 26	74-75.5	2250, 1740, 1580, 1350, 1300, 1140
$(CH_2)_3CO_2C_2H_5$	CN	CH_3	0	Ref. Ex. 32	oil	2240, 1730, 1580, 1210
			2	Ex. 27	73-75.5	2260, 1740, 1570, 1350, 1300, 1190, 1150
CH_2CN	CN	CH_3	0	Ref. Ex. 33	oil	2250, 1580, 1300, 1130
			2	Ex. 28	91.5-92.5	2260, 1570, 1360, 1300, 1140
$(CH_2)_2CN$	CN	CH_3	0	Ref. Ex. 34	oil	2240, 1580, 1300, 1130
			2	Ex. 29	oil	2250, 1570, 1360, 1300, 1150
$(CH_2)_3CN$	CN	CH_3	0	Ref. Ex. 35	oil	2240, 1580, 1120, 1080
			2	Ex. 30	oil	2250, 1580, 1350, 1300, 1140
CH_2CO-Ph	CN	CH_3	0	Ref. Ex. 36	81.5-82.5	2240, 1680, 1600, 1580, 1200, 690
			2	Ex. 31	133.5-134.5	2250, 1710, 1350, 1140, 760
$(CH_2)_2$-Cl	CN	CH_3	0	Ref. Ex. 37	oil	2930, 2240, 1580, 1490, 1300, 1260, 1120
			2	Ex. 32	157-158.5	3090, 2960, 2250, 1930, 1570, 1490, 1400, 1340, 1300, 1250, 1140
$(CH_2)_2$-OCH_3	CN	CH_3	0	Ref. Ex. 38	62.5-63.5	2960, 2240, 1610, 1580, 1510, 1440, 1300, 1250, 1180, 1120
			2	Ex. 33	155-156.5	2920, 2250, 1610, 1570, 1510, 1350, 1300, 1250, 1150
$(CH_2)_2$-NO_2	CN	CH_3	0	Ref. Ex. 39	90-91	2240, 1610, 1570, 1520, 1340, 1120
			2	Ex. 34	145-146.5	3080, 2980, 2260, 1600, 1570, 1510, 1430, 1350, 1300, 1240, 1180, 1140

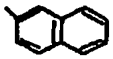
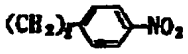
[Table 9]



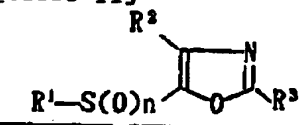
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	0	Ref. Ex. 40	81-82	3030. 2240. 1580. 1490. 1410. 1380. 1300. 1260. 1130
			2	Ex. 35	162-163	3000. 2250. 1570. 1490. 1340. 1310. 1190. 1150
	CN	CH_3	0	Ref. Ex. 41	oil	3380. 2240. 1580. 1500. 1280
			2	Ex. 36	200-201	3370. 2260. 1590. 1340. 1140
	CN	CH_3	0	Ref. Ex. 42	83-84	2240. 1580. 1250
			2	Ex. 37	156-157	2250. 1590. 1350. 1270. 1150
	CN	CH_3	0	Ref. Ex. 43	oil	2240. 1590. 1490. 1230
			2	Ex. 38	118-119	2250. 1590. 1350. 1150
	CN	CH_3	0	Ref. Ex. 44	89-90	2240. 1570. 1470
			2	Ex. 39	134-136	2250. 1560. 1350. 1150
	CN	CH_3	0	Ref. Ex. 45	135-137	2240. 1580. 1520. 1340. 1080
			2	Ex. 40	188-189	2250. 1610. 1580. 1540. 1360. 1160
	CN	CH_3	0	Ref. Ex. 46	oil	2240. 1580. 1490. 1120
			2	Ex. 41	117-118	2250. 1580. 1350. 1160
	CN	CH_3	0	Ref. Ex. 47	66-67	2240. 1610. 1570. 1330. 1120
			2	Ex. 42	127-129	2250. 1580. 1320. 1160
	CN	CH_3	0	Ref. Ex. 48	67.5-68.5	2240. 1580. 1480. 1090
			2	Ex. 43	132-132.5	2255. 1580. 1350. 1150
	CN	CH_3	0	Ref. Ex. 49	oil	2240. 1580. 1460. 1300. 1130
			2	Ex. 44	138-140	2250. 1570. 1350. 1300. 1160

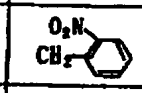
[Table 10]



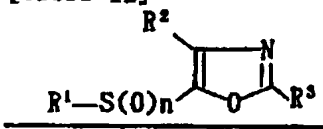
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	0	Ref. Ex. 50	72-73.5	2240. 1580. 1300. 1120
			2	Ex. 45	148-150	2250. 1620. 1580. 1560. 1350. 1150. 1130
$n-C_5H_{11}$	CN		0	Ref. Ex. 51	oil	2960. 2240. 1740. 1570. 1500. 1300. 1110
			2	Ex. 46	69-69.5	3000. 2960. 2250. 1560. 1500. 1460. 1340. 1280. 1150
	CN		0	Ref. Ex. 52	oil	3070. 3030. 2240. 1600. 1520. 1350. 1110
			2	Ex. 47	155-156	3070. 2960. 2250. 1600. 1560. 1520. 1450. 1350. 1270. 1160. 1130
$(CH_2)_2CO_2C_2H_5$	$CONHCH_2Ph$	CH_3	0	Ref. Ex. 53	oil	3400. 1730. 1660. 1570. 1510
			2	Ex. 48	107-107.5	3290. 1730. 1660. 1570. 1530. 1340. 1130
CH_3	CN	CF_3	0	Ref. Ex. 54	oil	2940. 2240. 1600. 1520. 1360. 1210. 1170. 1120
			2	Ex. 49	115-116	3030. 2930. 2260. 1590. 1340. 1280. 1170. 1130
C_3H_7	CN	CF_3	0	Ref. Ex. 55	oil	2970. 2240. 1590. 1520. 1360. 1210. 1170. 1120
			2	Ex. 50	oil	2980. 2260. 1590. 1460. 1370. 1270. 1220. 1180. 1130

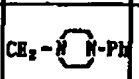
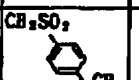
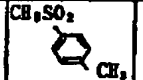
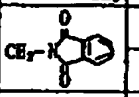
[Table 11]



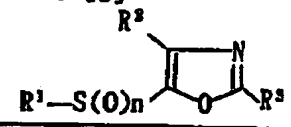
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
$n-C_5H_{11}$	CN	CF_3	0	Ref. Ex. 56	oil	2960, 2240, 1590, 1520, 1470, 1360, 1220, 1170
			2	Ex. 51	57-57.5	2960, 2260, 1590, 1370, 1270, 1220, 1180, 1140
Ph	CN	CF_3	0	Ref. Ex. 57	oil	2250, 1590, 1520, 1480, 1440, 1360, 1210, 1170, 1120
			2	Ex. 52	141-142	2260, 1580, 1560, 1450, 1380, 1210, 1170, 1140
CH_3	CN	CF_2CF_3	0	Ref. Ex. 58	oil	2940, 2240, 1580, 1440, 1330, 1220, 1140
			2	Ex. 53	121.5-122.5	3040, 2940, 2270, 1580, 1350, 1220, 1150
CH_3	CN	OCH_3	0	Ref. Ex. 59	oil	2950, 2240, 1620, 1550, 1430, 1350, 1290, 1120
			2	Ex. 54	105-106.5	3030, 2930, 2250, 1620, 1570, 1430, 1350, 1280, 1190, 1140
CH_3	CN	$NHCH_2CO_2$-C_4H_9(n)	0	Ref. Ex. 60	oil	3340, 2960, 2240, 1750, 1640, 1370, 1290, 1210, 1140
			2	Ex. 55	103.5-114.5	3330, 2970, 2260, 1750, 1650, 1550, 1340, 1220, 1140
CH_3	CN		2	Ex. 56-A	148-150	2250, 1520, 1350, 1340, 1160
CH_3	CN		2	Ex. 56-B	139.5-140.5	2250, 1730, 1570, 1530, 1350, 1150
CH_3	CN		2	Ex. 57	oil	3460, 3380, 2250, 1520, 1340, 1160
CH_3	CN	Br	2	Ex. 58	151.5-153.5	2260, 1480, 1330, 1280, 1160, 1130, 970, 780
CH_3	CN	$NHCH_3$	2	Ex. 59	195-196.5	3240, 3180, 3120, 2250, 1690, 1330, 1140

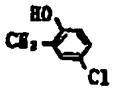
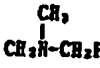
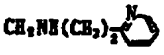
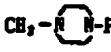
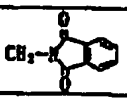
[Table 12]



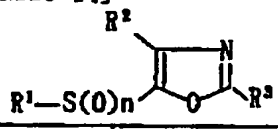
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
CH_3	CN	CH_3 N-CH_2Ph	2	Ex. 60	oil	2250. 1650. 1340. 1300. 1140
CH_3	CN		2	Ex. 61	175.5-176.5	3230. 3170. 2250. 1660. 1340. 1140. 970
CH_3	CN	CH_3 CH_2N-CH_2Ph	2	Ex. 62	oil	2250. 1570. 1350. 1150. 960. 770
CH_3	CN		2	Ex. 63	126.5-128	2250. 1600. 1350. 1230. 1150
CH_3	CN		2	Ex. 64-A	168-169	2260. 1560. 1340. 1310. 1160. 1090
	CN		2	Ex. 64-B	211-212.5	2250. 1350. 1320. 1160
CH_3	CN		0	Ref. Ex61	157-159.5	2230. 1780. 1720. 1420. 1400. 950
			2	Ex. 65	210.5 (analysis)	2250. 1780. 1730. 1340. 1150. 940
CH_3	$CONH_2$	CH_3	2	Ex. 66	227-228.5	3440. 3200. 1690. 1570. 1400. 1330. 1170. 1140. 970
CH_3	$CONH_2$	Ph	2	Ex. 67	210.5-212	3430. 3170. 1690. 1330. 1310. 1150
CH_3	CO_2H	CH_3	2	Ex. 68	191-192	2300-3100. 1740. 1725. 1580. 1570. 1330. 1145
CH_3	$CONHCH_2Ph$	CH_3	2	Ex. 69	145-146	3380. 1670. 1570. 1510. 1330. 1140
CH_3	$CONHC_4H_9(n)$	CH_3	2	Ex. 70	87-89	3350. 3310. 1670. 1580. 1520. 1330. 1140
CH_3		CH_3	2	Ex. 71	143-144	1640. 1560. 1320. 1130
CH_3		CH_3	2	Ex. 72	146.5-148	3390. 1680. 1580. 1510. 1340. 1310. 1130
CH_3		CH_3	2	Ex. 73	117-118	3270. 1660. 1590. 1570. 1520. 1320

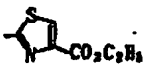
[Table 13]



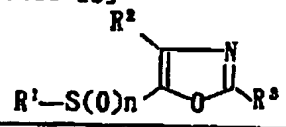
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
CH_3		CH_3	2	Ex. 74	116.5-118	1650. 1600. 1560. 1340. 1140
CH_3	CH_2OH	CH_3	0	Ref. Ex. 62	49-51	3350. 1570
CH_3	CH_2O-CO-Ph	CH_3	0	Ref. Ex. 63	oil	1720. 1580
			2	Ex. 75	100-100.5	1720. 1610. 1580. 1330. 1140
CH_3		CH_3	0	Ref. Ex. 64-A	oil	1580. 1490
			2	Ex. 76	123-124	1600. 1570. 1490. 1320
CH_3		CH_3	0	Ref. Ex. 64-A	144-146	2800-3200. 1590. 1560. 1500. 1140
			2	Ex. 77	165.5-167	3150. 1590. 1560. 1500. 1320. 1130
CH_3	CH_2Br	CH_3	0	Ref. Ex. 65	oil	1580. 1430. 1100. 780
			2	Ex. 78	103-103.5	1590. 1560. 1320. 1130
CH_3		CH_3	2	Ex. 79	oil	1570. 1490. 1330. 1130
CH_3		CH_3	2	Ex. 80	oil	3410. 1590. 1570. 1320. 1140
CH_3		CH_3	2	Ex. 81	112	1600. 1560. 1510. 1330. 1140. 760
CH_3		CH_3	2	Ex. 82	220-221	1770. 1720. 1600. 1340. 1320. 1130
CH_3		CH_3	2	Ex. 83	162-163	1590. 1560. 1320. 1140
CH_3	CO-C_4H_9(n)	CH_3	0	Ref. Ex. 66	oil	1670. 1520. 1150
			2	Ex. 84	oil	1700. 1580. 1340. 1180
Ph	CH_2OH	CH_3	0	Ref. Ex. 67	79-80	3330. 1570. 1480. 1020
Ph	CH_2Cl	CH_3	0	Ref. Ex. 68	oil	1580. 1480. 780. 740
			2	Ex. 85	106	1580. 1340. 1330. 1150. 730

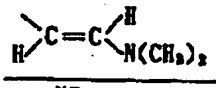
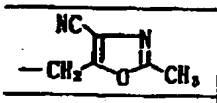
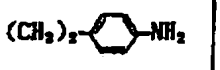
[Table 14]



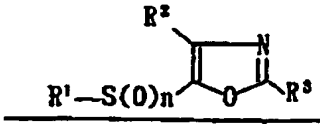
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
Ph	CH_2CN	CH_3	0	Ref. Ex. 69	oil	2260. 1580. 1570. 1480. 740
			2	Ex. 86	102.5-103	2260. 1590. 1570. 1340. 1150. 730
Ph	CH_2CO_2H	CH_3	2	Ex. 87	157-159	2800-3200. 1740. 1600. 1570. 1340. 1150. 730
CH_3	$CS-NH_2$	CH_3	2	Ex. 88	158-159	3390. 3320. 3210. 1630. 1570. 1320. 1140
CH_3	$CS-NHCH_2Ph$	CH_3	2	Ex. 89	oil	3310. 1580. 1570. 1510. 1330. 1170. 1140
CH_3	$CS-NHC_4H_9(n)$	CH_3	2	Ex. 90	88-89	3320. 1570. 1530. 1330. 1130
CH_3		CH_3	2	Ex. 91	176-178	1590. 1560. 1510. 1330. 1140
CH_3		CH_3	2	Ex. 92	121-122.5	3280. 1560. 1540. 1330. 1130
$n-C_5H_{11}$	$CS-NH_2$	CH_3	2	Ex. 93	oil	3410. 3310. 3200. 1610. 1580. 1330. 1130
CH_3	$CS-NH_2$	CH_2Ph	2	Ex. 94	149-150	3380. 3270. 3160. 1620. 1560. 1500. 1340. 1170
Ph	$CS-NH_2$	CH_3	2	Ex. 95	126.5-128	3400. 3310. 3180. 1620. 1580. 1330. 1150
CH_3		CH_3	2	Ex. 96	180-181	1580. 1330. 1160. 770. 750
CH_3		CH_3	2	Ex. 97	159.5-160.5	1730. 1570. 1320. 1170. 770

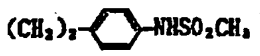
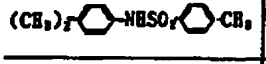
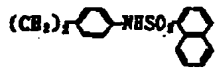
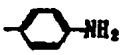
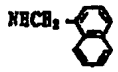
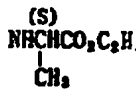
[Table 15]



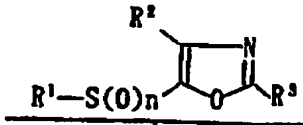
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
CH_2CO_2H	CN	CH_3	0	Ref. Ex. 70	75-76.5	2940. 2240. 1720. 1590. 1560. 1390. 1310. 1190. 1130
			2	Ex. 98	83.5-84.5	2970. 2250. 1730. 1560. 1430. 1340. 1140
$CH_2CONHC_4H_9(i)$	CN	CH_3	0	Ref. Ex. 71	oil	3310. 2960. 2240. 1650. 1550. 1470. 1390. 1300. 1260. 1160. 1120
			2	Ex. 99	111-112	3320. 2960. 2250. 1660. 1570. 1470. 1350. 1300. 1250. 1190. 1160
$(CH_2)_2CO_2CH_3$	CN	CH_3	0	Ref. Ex. 72	55-56	2990. 2930. 2250. 1740. 1570. 1440. 1350. 1300. 1270. 1200. 1140
$(CH_2)_2CO_2H$	CN	CH_3	0	Ref. Ex. 73	60-62	2970. 2250. 1740. 1560. 1430. 1340. 1270. 1140
$(CH_2)_2CONHC_4H_9(i)$	CN	CH_3	0	Ref. Ex. 74	oil	3310. 2960. 2240. 1650. 1550. 1470. 1260. 1120
			2	Ex. 100	113.5-115	3320. 2940. 2260. 1650. 1570. 1430. 1340. 1300. 1140
	CN	CH_3	2	Ex. 101	118.5-120.5	2250. 1630. 1320. 1120
	CN	CH_3	2	Ex. 102	150-151	2990. 2240. 1580. 1360. 1300. 1260. 1220. 1150. 1090
	CN	CH_3	2	Ex. 103	152-153	3430. 3350. 2910. 2250. 1630. 1570. 1520. 1450. 1350. 1320. 1150

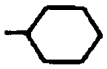
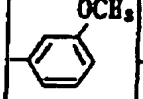
[Table 16]



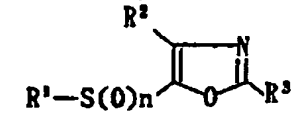
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	2	Ex. 104	137-138	3320, 3020, 2930, 2250, 1610, 1570, 1520, 1470, 1400, 1340, 1150
	CN	CH_3	2	Ex. 105	142-143	3240, 2250, 1570, 1510, 1480, 1410, 1340, 1300
	CN	CH_3	2	Ex. 106	169-170	3320, 2250, 1620, 1570, 1520, 1460, 1390, 1350, 1290, 1160, 1130
	CN	CH_3	2	Ex. 107	178-180	2240, 1640, 1590, 1330, 1150
$NHCH_2CH(CH_3)_2$	CN	CH_3	2	Ex. 108	80-81	3290, 2970, 2250, 1580, 1430, 1360, 1160
$NHCH_2Ph$	CN	CH_3	2	Ex. 109	109-110	3160, 2880, 2250, 1570, 1460, 1360, 1300, 1160
	CN	CH_3	2	Ex. 110	187-188	3160, 2250, 1570, 1430, 1370, 1300, 1160
NH-(1-adamantyl)	CN	CH_3	2	Ex. 111	155.5-157.0	3180, 2910, 2850, 2240, 1570, 1460, 1360, 1300, 1260, 1160
	CN	CH_3	2	Ex. 112	oil	3260, 2990, 2250, 1740, 1580, 1440, 1370, 1300, 1210, 1170, 1140
CH_3	CH_2Br	CH_3	1	Ex. 113	95-97	1580, 1030
Ph	CN	CH_3	1	Ex. 114	oil	2250, 1580, 1450, 1290, 1090, 1060
CH_2CN	CN	CH_3	1	Ex. 115	99.5-101.5	2250, 1580, 1290, 1060

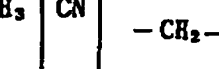
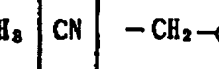
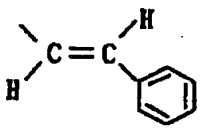
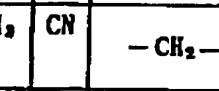
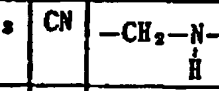
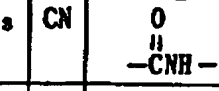
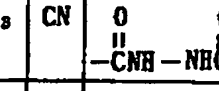
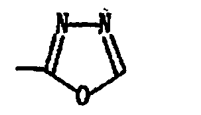
[Table 17]



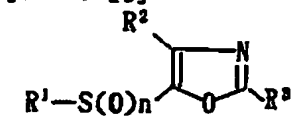
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
CH_3	CN	$C(CH_3)_3$	0	Ref. Ex. 75	46-47.5	2240, 1570, 1120
			2	Ex. 116	114.5-115.5	2240, 1570, 1550, 1340, 1150, 1130
CH_3	CN	CO_2CH_3	0	Ref. Ex. 76	70-71	3010, 2250, 1750, 1560
			2	Ex. 117	oil	3010, 2930, 2260, 1750, 1560, 1350, 1160
CH_3	CN	CH_2OCCH_3 (O)	1	Ex. 118	oil	3500, 2250, 1750, 1590, 1220, 1070
			2	Ex. 119	79-80	3040, 2250, 1750, 1580, 1340, 1220, 1150
CH_3	CN		0	Ref. Ex. 77	57-58	2940, 2240, 1560, 1060
			2	Ex. 120	111-112	2930, 2250, 1550, 1340, 1140, 960
CH_3	CN		0	Ref. Ex. 78	50-51.5	2240, 1580, 1310, 1070
			2	Ex. 121	138-139	2260, 1570, 1330, 1280, 1140
CH_3	CN	 (OCH_3)	1	Ex. 122	99-100	2240, 1550, 1490, 1220, 1040
			2	Ex. 123	156-158	2250, 1590, 1480, 1330, 1150, 1040
$-CH_2-C\equiv CH$	CN	CH_3	1	Ex. 124	oil	3300, 2240, 1680, 1270, 1080
			2	Ex. 125	oil	3200, 2250, 1580, 1350, 1160
CH_3	CO_2CH_3	CH_2Ph	2	Ex. 126	98-100	1740, 1570, 1340, 1320, 1070

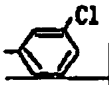
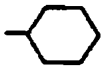
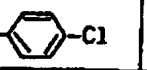
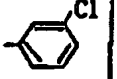
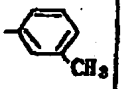
[Table 18]



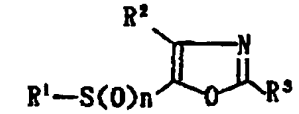
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
CH_3	CN		0	Ref. Ex. 79	oil	2240. 1610. 1520. 1250. 1040
			2	Ex. 127	100-102	2260. 1610. 1560. 1520. 1330. 1160. 970
CH_3	CN		0	Ref. Ex. 80	oil	2240. 1490. 1090. 1020
			2	Ex. 128	139-142	2250. 1490. 1340. 1160. 990. 780
CH_3	CN		0	Ref. Ex. 81	101-103	2230. 1540. 960
			1	Ex. 129	126-131	2250. 1630. 1530. 1060. 970. 770
			2	Ex. 130	183-186	2260. 1640. 1530. 1340. 1150. 960
CH_3	CN		2	Ex. 131	99-100	2980. 2250. 1570. 1340. 1150. 1110
CH_3	CN		2	Ex. 132	107-108	2900. 2250. 1570. 1330. 1140. 960
CH_3	CN		2	Ex. 133	84-85	3340. 2260. 1570. 1340. 1160. 960
CH_3	CN		0	Ref. Ex. 82	167-168	3360. 2240. 1680. 1600. 1350. 1150
CH_3	CN		0	Ref. Ex. 83	141-142	3320. 2240. 1680. 1550. 1500. 1130
CH_3	CN		0	Ref. Ex. 84	61-62	3150. 2240. 1630. 1500. 1130. 1090
			1	Ex. 134-A	101-102	3120. 2250. 1630. 1490. 1330. 1080
			2	Ex. 134-B	173-174	3170. 2260. 1630. 1340. 1140. 1100

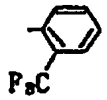
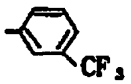
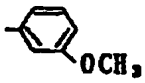
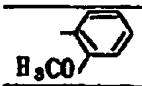
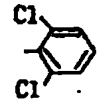
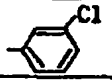
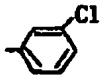
[Table 19]



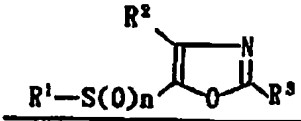
R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
	$CS-NH_2$		1	Ex. 135	90-93	3300, 2930, 1620, 1570, 1040
CH_3	$CS-NH_2$		2	Ex. 136	135-137	3430, 3300, 1610, 1510, 1325, 1250, 1160
CH_3	$CS-NH_2$		2	Ex. 137	168-170	3370, 3260, 3150, 1630, 1410, 1340, 1160
	$CS-NH_2$	CH_3	1	Ex. 138	170- (analysis)	1640, 1580, 1270, 1040
			2	Ex. 139	128- (analysis)	3420, 1620, 1570, 1340, 1180
Ph	CO_2H	CH_3	2	Ex. 140	74-78	1800-3600, 1730, 1570, 1350, 1170, 1150
Ph.	$NHCO_2C(CH_3)_3$	CH_3	2	Ex. 141	117-119	3200-3400, 1750, 1620, 1330, 1150, 730
Ph	CN	$C(CH_3)_3$	0	Ref. Ex. 85	oil	2240, 1560, 1120, 740
			2	Ex. 142	131-132	2250, 1550, 1350, 1160, 760, 730
	CN	CH_3	0	Ref. Ex. 86	oil	2240, 1580, 1300, 1120
			2	Ex. 143	125-126	2250, 1570, 1350, 1300, 1150
	CN	CH_3	0	Ref. Ex. 87	oil	2240, 1580, 1120
			2	Ex. 144	121-122.5	2250, 1570, 1350, 1160
	CN	CH_3	0	Ref. Ex. 88	oil	2240, 1580, 1460, 1300, 1130
			2	Ex. 145	138-140	2250, 1570, 1350, 1300 1160
	CN	CH_3	0	Ref. Ex. 89	oil	2240, 1580, 1480
			2	Ex. 146	91-92	2250, 1570, 1500, 1350, 1300, 1230, 1150

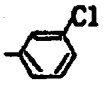
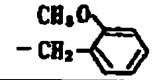
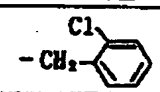
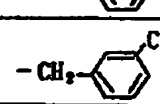
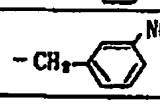
[Table 20]



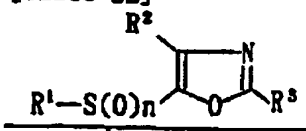
R^1	R	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	0	Ref. Ex. 90	oil	2240. 1580. 1310
			1	Ex. 147	oil	2250. 1580. 1320. 1130
			2	Ex. 148	130-132	2250. 1570. 1360. 1300. 1160. 1120
	CN	CH_3	0	Ref. Ex. 91	oil	2240. 1580. 1320
			2	Ex. 149	112-113.5	2260. 1570. 1330. 1300. 1160. 1130
	CN	CH_3	0	Ref. Ex. 92	oil	2240. 1580. 1480. 1260. 1120
			2	Ex. 150	128-129	2250. 1600. 1570. 1480. 1390. 1150
	CN	CH_3	0	Ref. Ex. 89	41-41.5	2240. 1590. 1480. 1250
			2	Ex. 151	138-140	2250. 1570. 1350. 1290. 1250. 1150
	CN	CH_3	0	Ref. Ex. 94	oil	2240. 1580. 1480. 1250
			2	Ex. 152	133-134	2250. 1570. 1350. 1160
	CN	CH_3	0	Ref. Ex. 95	125-126	2240. 1580. 1440. 1410. 780
			2	Ex. 153	119-121	2250. 1570. 1360. 1180. 1160
	CN	CH_3	0	Ref. Ex. 96	116-118	2240. 1590. 1430. 1130
			2	Ex. 154	109-111	2250. 1570. 1430. 1370 1300. 1200. 1160
	CN	CH_3	1	Ex. 155	oil	2240. 1580. 1290. 1090
	CN		0	Ref. Ex. 97	oil	2240. 1570. 1460. 1120
			1	Ex. 156	75-76	2250. 1560. 1270. 1070
			2	Ex. 157	132-133	2260. 1570. 1350. 1170
	CN	CH_3	0	Ref. Ex. 98	oil	2240. 1560. 1380
			1	Ex. 158	oil	2250. 1570. 1380. 1090
			2	Ex. 159	107-108	2250. 1570. 1360. 1130

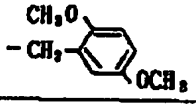
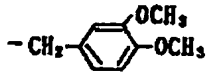
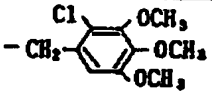
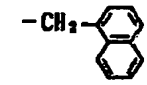
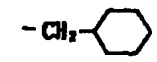
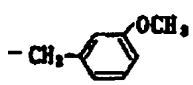
[Table 21]



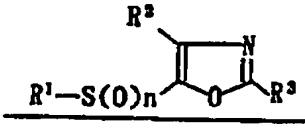
R^1	R	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
$-CH_2CH(CH_3)_2$	CN	CH_3	0	Ref. Ex. 99	oil	2240, 1580, 1260, 1120
			2	Ex. 160	75-76	2250, 1570, 1330, 1140
	CN	CH_3	0	Ref. Ex. 100	oil	2930, 2240, 1580, 1450, 1110
			1	Ex. 161	oil	2930, 2240, 1580, 1290, 1060
			2	Ex. 162	133-135	2250, 1570, 1330, 1140
	CN		0	Ref. Ex. 101	oil	2930, 2240, 1560, 1460, 1110
			1	Ex. 163	77-78.5	2930, 2240, 1560, 1460, 1100
			2	Ex. 164	84.5-85.5	2940, 2240, 1560, 1460, 1360, 1170
Ph	CO_2CH_3	CH_3	2	Ex. 165	108-109	1740, 1580, 1310, 1150, 730
	CN	CH_3	0	Ref. Ex. 102	oil	2240, 1580, 1460, 1300, 1120
			1	Ex. 166	oil	2240, 1570, 1290, 1100
			2	Ex. 167	141-143	2250, 1560, 1350, 1160
CH_3	CN		2	Ex. 168	87-89	2250, 1490, 1350, 1250, 1140
CH_3	CN		2	Ex. 169	118-120	2260, 1560, 1350, 1150, 970, 760
CH_3	CN		2	Ex. 170	94-97	2250, 1340, 1330, 1160, 990
CH_3	CN		2	Ex. 171	98-102	2240, 1520, 1350, 1340, 1160, 980

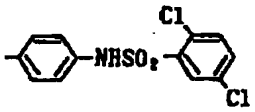
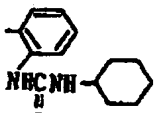
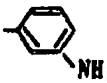
[Table 22]



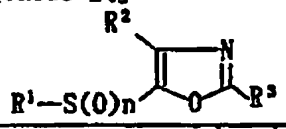
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
CH_3	CN		2	Ex. 172	154-157	2250. 1510. 1340. 1230. 1150. 1035
CH_3	CN		2	Ex. 173	128-130	2250. 1520. 1330. 1140
CH_3	CN		2	Ex. 174	108-117	2260. 1490. 1340. 1330. 1140. 1100
CH_3	CN		2	Ex. 175	114-117	2240. 1560. 1350. 1160
CH_3	CN		2	Ex. 176	145-148	2240. 1560. 1350. 1160
CH_3	CN		2	Ex. 177	110-113	2250. 1560. 1340. 1160. 1140
CH_3	CN		1	Ex. 178	97-99	2240. 1560. 1040
CH_3	CN		2	Ex. 179	93-95	2250. 1330. 1320. 1160. 1140
CH_3	CN	1-adamantyl	2	Ex. 180	157-160	2250. 1550. 1340. 1150

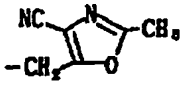
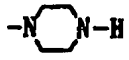
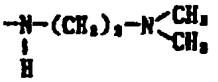
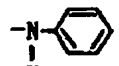
[Table 23]



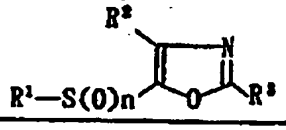
R^1	R^2	R^3	n	No.	m. p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	0	Ref. Ex. 103	96-97	3440, 3360, 2250, 1650, 1600, 1580, 1500
	CN	CH_3	0	Ref. Ex. 104	135-136	3320, 2240, 1630
			2	Ex. 181	180-181.5	3370, 3300, 2250, 1670, 1540, 1350, 1150
	CN	CH_3	0	Ref. Ex. 105	115-116	3280, 3230, 2230, 1600, 1340, 1320, 1150
			2	Ex. 182	182-184	3270, 2260, 1600, 1330, 1140
	CN	CH_3	0	Ref. Ex. 106	160-162	3270, 2240, 1340, 1170
			2	Ex. 183	234-235	3280, 2250, 1590, 1580, 1340, 1150
	CN	CH_3	0	Ref. Ex. 107	oil	3470, 3370, 2240, 1620, 1480, 750
	CN	CH_3	0	Ref. Ex. 108	172-174	3320, 2240, 1640, 1580
			1	Ex. 184	152-153	3290, 2250, 1640, 1570, 1290
			2	Ex. 185	224-226	3330, 2250, 1660, 1580, 1350, 1150
	CN	CH_3	0	Ref. Ex. 109	216-218	3310, 2240, 1630
			2	Ex. 186	210~ (analysis)	3320, 1630, 1570, 1340, 1155
	CN	CH_3	0	Ref. Ex. 110	oil	3470, 3370, 2240, 1590, 1480

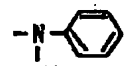
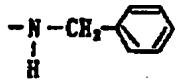
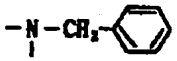
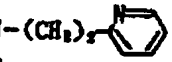
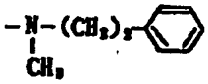
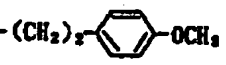
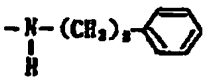
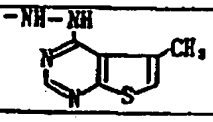
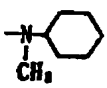
[Table 24]



R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	0	Ref. Ex. 111	123.5-124.5	2240, 1650, 1590, 1550
			2	Ex. 187	151~ (glass transition)	3300, 2250, 1650, 1350, 1150
	CN		2	Ex. 188	148-149	2240, 1560, 1350, 1160
$-NH_2$	CN	CH_3	2	Ex. 189	164-165	3180, 2250, 1580, 1360, 1170
	CN	CH_3	2	Ex. 190	59-60	2250, 1580, 1370, 1300, 1150
	CN	CH_3	2	Ex. 191	oil	2950, 2250, 1580, 1370, 1270, 1170
	CN	CH_3	2	Ex. 192	115-116	3330, 2250, 1580, 1360, 1160
	CN	CH_3	2	Ex. 193	145-146.5	3400, 2250, 1590, 1350, 1150
	CN	CH_3···	2	Ex. 194	147-148	3090, 2250, 1570, 1430, 1370, 1300, 1170

[Table 25]



R^1	R^2	R^3	n	No.	m.p. (℃)	IR Spectrum(cm^{-1})
	CN	CH_3	2	Ex. 195	121-123	2250, 1580, 1490, 1380, 1300, 1190, 1150
	CN	CH_3	2	Ex. 196	171-172	3200, 2250, 1570, 1360, 1300, 1160
	CN	CH_3	2	Ex. 197	83-84	2250, 1580, 1370, 1300, 1150
	CN	CH_3	2	Ex. 198	121-122.5	3010, 2250, 1580, 1360, 1300, 1160, 1080
	CN	CH_3	2	Ex. 199	oil	2250, 1580, 1370, 1300, 1150
	CN	CH_3	2	Ex. 200	113-114	3290, 2250, 1580, 1360, 1300, 1150
	CN	CH_3	2	Ex. 201	81-82	3210, 2250, 1580, 1510, 1370, 1160
	CN	CH_3	2	Ex. 202	80-81	3290, 2250, 1580, 1420, 1370, 1160
	CN	CH_3	2	Ex. 203	185-187	3270, 2250, 1630, 1580, 1310, 1140
	CN	CH_3	2	Ex. 204	155.5-156	2880, 2250, 1580, 1380, 1160, 1110
	CN	CH_3	2	Ex. 205	85	2920, 2250, 1590, 1370, 1150, 1000

[Experimental Example 1]
Inhibition of IL-6 activity

The test compoundwas dissolved in N,N-dimethylformamide at a concentration of 10 mM and this solution was diluted with RPMI-1640 medium at a final concentration of 0.1 mM. Then, this dilution was further diluted serially with the same medium by the doubling dilution method to provide a concentration series from 20 μM to 0.16 μM for addition to the culture system.

Using the IL-6-dependent cell line MH60, the inhibitory effect of the test compound on IL-6-dependent growth of cells was evaluated. On the day immediately preceding the experiment, the cells were suspended in 10% inactivated fetal calf serum-RPMI-1640 medium at a density of $1x10^5$/mL and grown in a flask at 37°C under sparging with 5% CO_2/95% air. On the day of starting the experiment, the cultured cells were seeded in a 96-well plate, at a density of $1x10^4$ cells/0.1 mL/well. After the test compound preparation was added to the wells, IL-6 was added at a final concentration of 0.25 ng/mL. After 2 days of incubation, 0.02 mL of solution of dimethylthiazolyl diphenyltetrazolium bromide (MTT) in PBS (5 mg/mL) was added to each well, and the plate was further incubated for 3 hours. Then, 0.1 mL of 10% sodium dodecyl sulfate 0.01N-HCl solution was added to each well and the plate was further incubated at 37°C overnight. Then, using the Multi-Scan, the optical density at 560 nm was measured to estimate the viability of cells.

As a result, the test compound was found to effectively inhibit growth of MH60 cells. The data are presented in Table 26 in terms of IC_{50} which is the concentration of the test compound causing 50% inhibition of growth.

Table 26

Ex. No. of test compound	IC_{50} (μM)
6	0.83
13	0.91
17	0.80
18	0.85
38	0.90
44	0.49
94	0.79
95	0.85
114	0.80
116	0.98
122	0.84
136	0.79
137	0.78
138	0.98
139	0.64
143	0.59
144	0.83
145	0.81
146	0.73
147	0.39
148	0.93
150	0.90
151	0.88
153	0.36
154	0.33
155	0.37
166	0.34
167	0.61
169	0.99
187	0.90
204	0.75

It is clear from the data shown in Table 26 that the oxazole derivatives of the present invention have excellent IL-6-inhibitory activity.

[Experimental Example 2]

Inhibition of acute-phase protein production

It is known that in the event of infection, tissue injury, development of a malignant tumor, or immunologic abnormality, the body reacts to such an event by producing acute-phase proteins and that IL-6 is the most crucial factor in the induction of such

proteins. In amyloidosis secondary to chronic inflammatory diseases, the acute-phase protein serum amyloid A protein becomes fibrillated and is deposited extracellularly to elicit disorders of the organs. Then, effect of the test compound on the production of serum amyloid A protein was investigated in experimental animals.

Female C57BL/6 mice (6 weeks old) were acclimatized for 1 week, and divided into groups of 5 animals. Mice in the test group were given a single dose of the test compound suspended in 5% aqueous arabic gum solution by oral gavage. A control group was similarly treated with the vehicle only. One hour after administration, 0.25 mg of LPS, the outer membrane fraction of Gram-negative bacteria, was administered intraperitoneally to animals in both the test group and the control group. The blood was drawn 7 hours after administration of LPS, and serum amyloid A protein concentration was determined by the sandwich ELISA method. The result is set forth in Table 27. The asterisk denotes significant difference from control ($p<0.01$; student t-test).

[Table 27]

treatment	dose (mg/kg)	Inhibition of serum amyloid A protein production (%)
none	0	0
compound of Ex. 6	50	54*
compound of Ex. 13	50	78*

It is clear from Table 27 that the oxazole derivatives of the present invention have excellent activity to inhibit the production of the acute-phase protein.

[0151]

[Experimental Example 3]

Inhibition of NO production

Using the mouse macrophage-derived cell line RAW 264.7 as iNOS-induction cells, the inhibitory effect of the test compound on NO production was evaluated. The test compound was dissolved in N,N-dimethylformamide at a concentration of 10 mM and the solution was diluted with RPMI-1640 medium to 0.1 mM. This solution was further diluted serially with the same medium by the 10-fold dilution method to provide a concentration series from 10 μM to about 10 nM for addition to the culture system. On the day immediately preceding the experiment, cells were suspended in 10% inactivated fetal calf serum-RPMI-1640 medium at a density of $5x10^5$/ml and seeded in a 96-well plate, $1x10^5$ cells/0.2 ml/well. The plate was incubated at 37°C under aeration with 5% CO_2/95% air overnight and then the test compound preparation was added. LPS and gamma interferon were then added at final concentrations of 5 ng/ml and 1 U/ml, respectively, and the plate was incubated. After overnight culture, the nitrite ion (stable metabolite of NO) in the culture supernatant was determined as an indicator of NO production. The nitrite ion concentration was measured by adding 25 μl of 2,3-diaminonaphthalene (DAN) (20 μg/ml) to 50 μl of culture supernatant and measuring the fluorescent emission at 450 nm (exciting wavelength 365 nm). The results are shown in Table 28. IC_{50} stands for the concentration of the test compound causing 50% inhibition of NO production.

[Table 28]

Ex. No. of test compound	IC_{50} (nM)
1	73
2	65
7	19
24	40
34	13
35	28
62	15
98	15
121	10
122	80
123	9.8
181	67
195	24
204	28
205	28

It is clear from Table 28 that the oxazole derivative of the present invention strongly inhibits release of NO from RAW264.7 cells and thus has excellent NO production-inhibitory activity.

[Experimental Example 4]

Effect against elevation of blood nitrogen oxide concentration

As NO is produced in the body as a defense against infection or immunologic abnormality, it is immediately metabolized into nitrous acid and nitric acid so that the blood nitrogen oxide (NOx) level is elevated. Therefore, using experimental animals, the effect of the test compound on this elevation of blood NOx concentration was evaluated.

Female BALB/c mice (6 weeks old) were acclimatized for 1 week, and divided into groups each consisting of 6-8 animals. The mice in the test group were intraperitoneally dosed with 30 mg/kg of the test compound (compound of Ex. 8, 88, 123 or 132) suspended in 0.5% aqueous methylcellulose solution. The control group received the vehicle only in the same manner. After 30 minutes, LPS (30 mg/kg) was administered

intraperitoneally to animals in both the test group and the control group. The blood was drawn 6 hours after LPS administration and the serum concentration of nitrate ion + nitrite ion was measured. The nitrate ion was converted to nitrite ion with nitrate reductase and the total nitrite ion concentration was determined by the above-mentioned fluorometry using DAN. The test compounds showed significant inhibition compared with control (student's t-test).

It is clear that the oxazole derivative of the present invention exerts excellent NO production-inhibitory activity in vivo as well.

The oxazole derivative of the present invention has excellent inhibitory activities of IL-6 activity and NO production can be used as a safe IL-6 activity inhibitor or NO production inhibitor in human and other mammalian animals (e.g. mouse, rat, guinea pig, rabbit, dog, cat, bovine, swine, sheep, monkey, chimpanzee). Furthermore, the oxazole derivative (I') can be used as a medicine, such as a prophylactic and therapeutic drug for IL-6-associated diseases, for example, cardiac diseases such as myocardiopathy, cardiac hypertrophy, myocardial infarction, angina pectoris, etc., various autoimmune diseases such as chronic rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, rheumatic fever, polymyositis, periarteritis nodosa, Sjögren's syndrome, Behcet's disease, Castleman's disease, autoimmune hemolytic anemia, etc., inflammatory diseases such as mesangial proliferative nephritis, IgA nephritis, lupus nephritis, osteoporosis, amyloidosis, bronchial asthma, atopic dermatitis, psoriasis, pleurisy, ulcerative colitis, atherosclerosis, active chronic hepatitis, alcoholic cirrhosis, gout, various types of encephalitis, etc., or diseases accompanied by

granuloma such as multiple myeoloma, atrial myxoma, renal carcinoma, pulmonary adenocarcinoma, malignant mesothelioma, ovarian cancer, cancerous cachexia, etc., or NO-associated diseases, for example, atherosclerosis, myocarditis, myocardiopathy, ischemic brain disorder, Alzheimer's disease, multiple sclerosis, septicemia, rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerulonephritis, osteoporosis, pneumonia, hepatitis, graft rejection, pain, etc., with safety in human and other mammalian animals (e.g. mouse, rat, guinea pig, rabbit, dog, cat, bovine, swine, sheep, monkey, chimpanzee).

CLAIMS

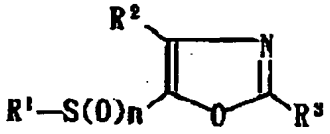
What is claimed is:

1. An oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, provided that when the substituent at the 4-position is hydrogen, (1) the compound which has 4-methoxyphenyl or 4-methoxyphenylethinyl at the 2-position and nonafluorobutylsulfonyl at the 5-position, (2) the compound which has phenyl at the 2-position and (2-phenyl-5-thiazolyl)sulfonyl at the 5-position, and (3) the compound which has 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methyl-1-(E)-propenyl at the 2-position and 4-methylphenylsulfonyl at the 5-position are excluded.

2. The oxazole derivative according to claim 1, which has a halogen atom or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom as a substituent at the 2-position of the oxazole ring.

3. The oxazole derivative according to claim 1, which has a halogen atom or a group bonded through a carbon, nitrogen, oxygen, or sulfur atom as a substituent at the 4-position of the oxazole ring.

4. The oxazole derivative according to claim 1, which is a compound of the formula:



(I)

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n

represents 1 or 2; R^2 represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted, or carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -S(O)m-R; where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2.

5. The oxazole derivative according to claim 4, wherein R^1 represents a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, or amino which may be substituted;
R^2 represents hydrogen, cyano, an organic carboxylic acid-derived acyl group, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, amino which may be substituted, or carboxyl which may be esterified;
R^3 represents hydrogen, halogen, a C_{1-19} hydrocarbon group which may be substituted, a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted, a C_{1-19} hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -

S(O)m-R'; where R' represents a C_{1-19} hydrocarbon group which may be substituted or a 5- to 8-membered heterocyclic group containing at least 1 atom selected from nitrogen, oxygen, and sulfur, which may be substituted; m represents 0, 1, or 2.

6. The oxazole derivative according to claim 4, wherein R^1 represents
(1) C_{1-19} alkyl which may be substituted with (i) a 5- or 6-membered sulfur-containing heterocyclic group, (ii) a 5- or 6-membered oxygen- and nitrogen-containing heterocyclic group which may be substituted with C_{1-12} alkyl or cyano, (iii) carboxyl, (iv) C_{6-14} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be mono- or di-substituted with C_{1-12} alkyl, or (vii) C_{1-12} alkoxy-carbonyl,
(2) C_{2-12} alkenyl which may be substituted with mono- or di-C_{1-12} alkylamino,
(3) C_{2-12} alkinyl,
(4) C_{3-10} cycloalkyl,
(5) C_{6-14} aryl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which may be substituted with C_{1-12} alkyl or C_{3-10} cycloalkyl, (b) C_{6-14} arylsulfonyl which may be substituted with halogen, or (c) C_{1-12} alkylsulfonyl, (iv) C_{1-12} alkyl which may be substituted with halogen, (v) nitro or (vi) hydroxyl,
(6) C_{7-19} aralkyl which may be substituted with (i) halogen, (ii) C_{1-12} alkoxy, (iii) amino which may be substituted with (a) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl or (b) C_{1-12} alkylsulfonyl, or (iv) nitro,
(7) a 5- or 6-membered nitrogen- or oxgen-containing heterocyclic group,
(8) amino which may be substituted with (i) C_{1-12} alkyl

which may be substituted with (a) C_{1-12} alkoxy-carbonyl, (b) mono- or di-C_{1-12} alkylamino or (c) a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{7-19} aralkyl which may be substituted with halogen or C_{1-12} alkoxy, (iii) C_{4-12} bridged-ring hydrocarbon group, (iv) C_{6-14} aryl or (v) C_{3-10} cycloalkyl or
(9) thienopyrimidylhydrazino which may be substituted with C_{1-12} alkyl.

7. The oxazole derivative according to claim 4, wherein R^1 represents
(1) C_{1-12} alkyl which may be substituted with (i) thienyl, (ii) oxazolyl which may be substituted with C_{1-6} alkyl or cyano, (iii) carboxyl, (iv) C_{6-12} arylcarbonyl, (v) cyano, (vi) carbamoyl which may be mono- or di-substituted with C_{1-6} alkyl, or (vii) C_{1-6} alkoxy-carbonyl,
(2) C_{2-6} alkenyl which may be substituted with mono- or di-C_{1-6} alkylamino,
(3) C_{2-6} alkinyl,
(4) C_{3-8} cycloalkyl,
(5) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) carbamoyl which is substituted with C_{1-6} alkyl or C_{3-8} cycloalkyl, (b) C_{6-12} arylsulfonyl which may substituted with halogen or (c) C_{1-6} alkylsulfonyl, (iv) C_{1-6} alkyl which may be substituted with halogen (v) nitro or (vi) hydroxy,
(6) C_{7-13} aralkyl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy, (iii) amino which may be substituted with (a) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl or (b) C_{1-6} alkylsulfonyl, or (iv) nitro,
(7) a heterocyclic group selected from the group

consisting of pyrimidyl, piperidino, morpholino and 1-piperazinyl,
(8) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with (a) C_{1-6} alkoxy-carbonyl, (b) mono- or di-C_{1-6} alkylamino or (c) pyridyl, (ii) C_{6-12} aryl, (iii) C_{7-13} aralkyl which may be substituted with halogen or C_{1-6} alkoxy, (iv) adamantyl or (v) C_{3-8} cycloalkyl, or
(9) thienopyrimidylhydrazino which may be substituted with C_{1-6} alkyl.

8. The oxazole derivative according to claim 4, wherein R^2 represents
(1) cyano,
(2) C_{1-12} alkanoyl,
(3) carbamoyl which may be substituted with (i) C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group, (ii) C_{1-12} alkoxy or (iii) C_{7-19} aralkyl,
(4) a 5- or 6-membered saturated nitrogen-containing heterocyclic-carbonyl, which may be substituted with C_{6-14} aryl,
(5) thiocarbamoyl which may be substituted with (i) C_{1-12} alkyl or (ii) C_{7-19} aralkyl,
(6) a 5- or 6-membered saturated nitrogen-containing heterocyclic-thiocarbonyl,
(7) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of (i) hydroxyl which may be acylated with C_{6-14} arylcarbonyl, (ii) halogen, (iii) carboxyl, (iv) cyano, (v) amino which may be substituted with C_{1-12} alkyl which may be substituted with a 5- or 6-membered nitrogen-containing heterocyclic group or C_{7-19} aralkyl, (vi) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms, which may be substituted with C_{6-14}

aryl, (vii) phthalimido, (viii) C_{6-14} arylsulfonyl which may be substituted with C_{1-12} alkyl, and (ix) C_{6-14} aryloxy which may be substituted with halogen,
(8) C_{7-19} aralkyl which may be substituted with halogen or hydroxyl,
(9) a 5- or 6-membered nitrogen and sulfur-containing heterocyclic group, which may be substituted with (i) C_{1-12} alkoxy-carbonyl or (ii) C_{6-14} aryl,
(10) amino which may be substituted with C_{1-12} alkoxy-carbonyl,
(11) carboxyl, or
(12) C_{1-12} alkoxy-carbonyl.

9. The oxazole derivative according to claim 4, wherein R^2 represents
(1) cyano,
(2) C_{1-6} alkanoyl,
(3) carbamoyl which may be substituted with (i) C_{1-6} alkyl which may be substituted with pyridyl, (ii) C_{7-13} aralkyl or (iii) C_{1-6} alkanoyl,
(4) piperidinocarbonyl,
(5) 1-piperazinylcarbonyl which may be substituted with C_{6-12} aryl,
(6) thiocarbamoyl which may be substituted with (i) C_{1-6} alkyl or (ii) C_{7-13} aralkyl,
(7) piperidinothiocarbonyl,
(8) C_{1-6} alkyl which may be substituted with (i) hydroxy which may be acylated with C_{6-12} arylcarbonyl, (ii) halogen, (iii) carboxyl, (iv) cyano, (v) amino which may substituted with (a) C_{1-6} alkyl which may be substituted with pyridyl or (b) C_{7-13} aralkyl, (vi) 1-piperazinyl which may be substituted with C_{6-12} aryl, (vii) phthalimido, (viii) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, or (ix) C_{6-12} aryloxy which may be substituted with halogen,

(9) C_{7-13} aralkyl which may be substituted with halogen or hydroxyl,
(10) thiazolyl which may be substituted with C_{1-6} alkoxy-carbonyl or (b) C_{6-12} aryl,
(11) amino which may be substituted with C_{1-6} alkoxy-carbonyl,
(12) carboxyl, or
(13) C_{1-6} alkoxy-carbonyl.

10. The oxazole derivative according to claim 4, wherein R^3 represents
(1) hydrogen,
(2) halogen,
(3) C_{1-12} alkyl which may be substituted with a group selected from the group consisting of (i) amino which may be substituted with C_{7-19} aralkyl or C_{1-12} alkyl, (ii) a 5- or 6-membered saturated heterocyclic group containing 2 nitrogen atoms which may be substituted with C_{6-14} aryl, (iii) phthalimido, (iv) C_{6-14} arylsulfonyl which may substituted with C_{1-12} alkyl, (v) hydroxyl which may be substituted with C_{1-12} alkanoyl, (vi) a 5- or 6-membered saturated nitrogen- and/or oxygen-containing heterocyclic group, (vii) halogen, (viii) C_{1-12} alkoxy-carbonyl,
and (ix) a 5- to 6-membered unsaturated nitrogen- and/or oxgen-containing heterocyclic group, which may be substituted with C_{1-6} alkyl or cyano,
(4) C_{2-12} alkenyl which may be substituted with C_{6-14} aryl,
(5) C_{6-14} aryl which may be substituted with C_{1-12} alkoxy,
(6) C_{7-19} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) C_{1-12} alkoxy, or (iv) halogen,
(7) C_{3-10} cycloalkyl,
(8) C_{3-10} cycloalkyl-C_{1-12} alkyl,
(9) a C_{4-12} bridged-ring hydrocarbon group,

(10) a 5- to 6-membered unsaturated nitrogen- and/or oxygen-containing heterocyclic group,
(11) C_{1-12} alkoxy,
(12) amino which may be substituted with (i) C_{1-12} alkyl which may substituted with C_{1-12} alkoxy-carbonyl or (b) a 5- or 6-membered nitrogen-containing heterocyclic group or (ii) C_{7-19} aralkyl, or
(13) C_{1-12} alkoxy-carbonyl.

11. The oxazole derivative according to claim 4, wherein R^3 represents
(1) hydrogen,
(2) halogen,
(3) C_{1-6} alkyl which may be substituted with (i) amino which may be substituted with C_{7-13} aralkyl or C_{1-6} alkyl, (ii) 1-piperazinyl which may be substituted with C_{6-12} aryl, (iii) phthalimide, (iv) C_{6-12} arylsulfonyl which may be substituted with C_{1-6} alkyl, (v) hydroxyl which may be substituted with C_{1-6} alkanoyl, (vi) morpholino, (vii) piperidino, (viii) halogen, (ix) C_{1-6} alkoxy-carbonyl, and (x) oxazolyl which may be substituted with C_{1-6} alkyl or cyano,
(4) C_{2-6} alkenyl which may be substituted with C_{6-12} aryl,
(5) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy,
(6) C_{7-13} aralkyl which may be substituted with (i) amino, (ii) nitro, (iii) C1-6 alkoxy, or (iv) halogen,
(7) C_{3-8} cycloalkyl,
(8) C_{3-8} cycloalkyl-C_{1-6} alkyl,
(9) adamantyl,
(10) oxadiazolyl,
(11) C_{1-6} alkoxy,
(12) amino which may be substituted with (i) C_{1-6} alkyl which may be substituted with C_{1-6} alkoxy-carbonyl or

pyridyl, or (ii) C_{7-13} aralkyl, or
(13) C_{1-6} alkoxy-carbonyl.

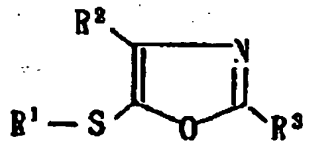
12. The oxazole derivative according to claim 4, wherein R^1 represents (1) C_{1-6} alkyl which may be substituted with (i) 2-thienyl or (ii) carboxyl, (2) C_{6-12} aryl which may be substituted with (i) halogen, (ii) C_{1-6} alkoxy or (iii) C_{1-6} alkylcarbamoylamino, (3) C_{7-13} aralkyl which may be substituted with nitro, (4) amino which may be substituted with (i) C_{1-6} alkyl, (ii) C_{6-12} aryl or (iii) C_{3-8} cycloalkyl, or (5) morpholino.

13. The oxazole derivative according to claim 4, wherein R^2 represents cyano, thiocarbamoyl, carbamoyl, or C_{1-6} alkyl which may be substituted with halogen.

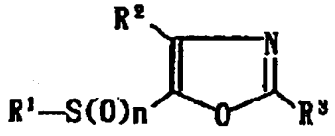
14. The oxazole derivative according to claim 4, wherein R^3 represents (1) hydrogen, (2) C_{1-6} alkyl which may be substituted with amino which may have C_{1-6} alkyl or C_{7-15} aralkyl substituent, (3) C_{3-6} cycloalkyl, (4) C_{6-12} aryl which may be substituted with C_{1-6} alkoxy or (5) C_{7-13} aralkyl which may be substituted with (i) halogen or (ii) C_{1-6} alkoxy.

15. The oxazole derivative according to claim 4, wherein n is 2.

16. A process for producing the oxazole derivative according to claim 4, which comprises
(1) oxidizing a compound of the formula:

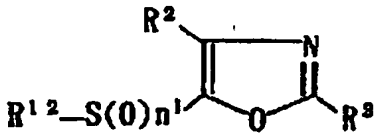


wherein R^1, R^2, and R^3 are as defined in claim 4 to give an oxazole derivative of the formula:



wherein R^1, R^2, and R^3 are as defined above, and n is as defined in claim 4,

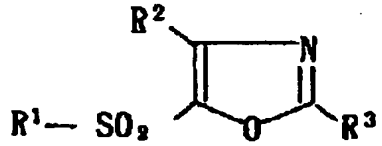
(2) reacting a compound of the formula:



wherein R^2 and R^3 are as defined above; R^{12} represents lower alkyl or phenyl; n^1 is 0, 1, or 2 with a compound of the formula:

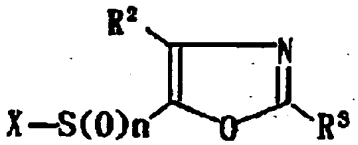
$$R^1\text{-}SO_2M$$

wherein R^1 is as defined above; M represents an alkali metal to obtain an oxazole derivative of the formula:



wherein R^1, R^2, and R^3 are as defined above, or

(3) reacting a compound of the formula:

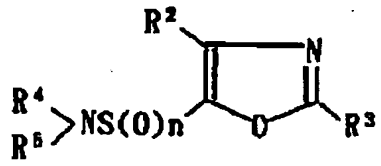


wherein R^2, R^3, and n are as defined above; X represents a leaving group with a compound of the

formula:

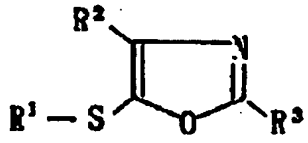
$$HNR^4R^5$$

wherein R^4 and R^5 independently represent hydrogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted; R^4 and R^5 may be combined with the adjacent nitrogen atom to form a heterocyclic group to obtain an oxazole derivative of the formula:



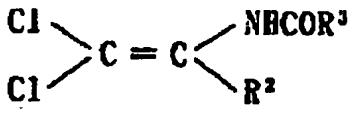
wherein R^2, R^3, n, R^4, and R^5 are as defined above.

17. A process for producing a compound of the formula:



wherein R^1, R^2, and R^3 are as defined in claim 4, which comprises

(1) reacting a compound of the formula:



wherein R^2 and R^3 are as defined above with a compound of the formula:

$$M_2S$$

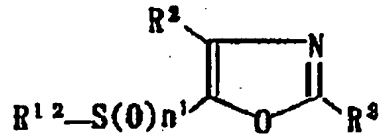
wherein M represents an alkali metal and a compound of the formula:

$$R^1X$$

wherein R^1 is as defined above; X represents a leaving

group, or

(2) reacting a compound of the formula:

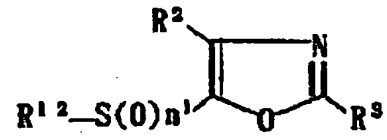


wherein R^2 and R^3 are as defined above; R^{12} represents lower alkyl or phenyl; n^1 is 0, 1, or 2 with a compound of the formula:

$$R^1\text{-}SH$$

wherein R^1 are as defined above, or

(3) reacting a compound of the formula:



wherein R^2, R^3, R^{12} and n^1 are as defined above with a compound of the formula:

$$M_2S$$

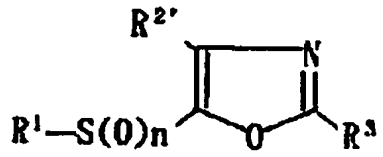
wherein M is as defined above and a compound of the formula:

$$R^1X$$

wherein R^1 and X are as defined above.

18. A pharmaceutical composition comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring.

19. The pharmaceutical composition according to claim 18, wherein the oxazole derivative is a compound of the formula:



(I')

wherein R^1 represents a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, or amino which may be substituted; n represents 1 or 2; $R^{2'}$ represents hydrogen, cyano, acyl, carbamoyl which may be substituted, thiocarbamoyl which may be substituted, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted, or carboxyl which may be esterified; R^3 represents hydrogen, halogen, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a hydrocarbon-oxy group which may be substituted, amino which may be substituted, carboxyl which may be esterified, or a group of the formula -S(O)m-R, where R represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; m represents 0, 1, or 2.

20. The pharmaceutical composition according to claim 18 or 19, which is a prophylactic or therapeutic pharmaceutical for cardiac diseases, autoimmune diseases, inflammatory diseases, or diseases accompanied by granuloma.

21. The pharmaceutical composition according to claim 18 or 19, which is a prophylactic or therapeutic pharmaceutical for myocardiopathy, cardiac hypertrophy, myocardial infarction, angina pectoris, chronic rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, rheumatic fever, polymyositis, periarteritis nodosa, Sjögren's syndrome, Behcet's

disease, Castleman's disease, autoimmune hemolytic anemia, mesangial proliferative nephritis, IgA nephritis, lupus nephritis, osteoporosis, amyloidosis, bronchial asthma, atopic dermatitis, psoriasis, pleurisy, ulcerative colitis, atherosclerosis, active chronic hepatitis, alcoholic cirrhosis, gout, encephalitis, multiple myeoloma, atrial myxoma, renal carcinoma, pulmonary adenocarcinoma, malignant mesothelioma, ovarian cancer or cancerous cachexia.

22. A composition for inhibition of interleukin-6 activity comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring.

23. The pharmaceutical composition according to claim 18 or 19, which is a prophylactic or therapeutic pharmaceutical for atherosclerosis, myocarditis, myocardiopathy, ischemic brain disorder, Alzheimer's disease, multiple sclerosis, septicemia, chronic rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerulonephritis, osteoporosis, pneumonia, hepatitis, graft rejection or pain.

24. A composition for inhibition of nitrogen monoxide production comprising an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring.

25. Use of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, for the manufacture of a medicament for inhibiting interleukin-6 activity.

26. Use of an oxazole derivative having a group bonded

through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, for the manufacture of a medicament for inhibiting nitrogen monoxide production.

27. A method for inhibiting interleukin-6 activity in human or mammal, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal.

28. A method for preventing or treating interleukin-6-associated diseases, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal.

29. A method for inhibiting nitrogen monoxide production in human or mammal, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal.

30. A method for preventing or treating nitrogen monoxide-associated diseases, which comprises administering an effective amount of an oxazole derivative having a group bonded through a sulfinyl or sulfonyl moiety at the 5-position of the oxazole ring, to human or the mammal.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/JP 96/03857

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/46 A61K31/42 C07D413/12 C07D495/04 C07D413/04
C07D417/04 C07D413/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 087 953 A (BEECHAM GROUP PLC) 7 September 1983 cited in the application see page 98 - page 99; examples 36,37	1
X	WO 95 24403 A (ZENECA LTD) 14 September 1995 see page 11 - page 14; claim 1	1
A	WO 95 13067 A (SMITHKLINE BEECHAM CORPORATION) 18 May 1995 see claims	1,18-30

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 1997	27.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/JP 96/03857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF GENERAL CHEMISTRY USSR, vol. 56, no. 7, 1986, NEW YORK US, pages 1323-1332, XP002028005 V.S.BROVARETS ET AL: "Reactions of substituted phosphinomethylene containing 2-alkyl(or aryl)-4,5-dihydro-5-thioxo-4-oxazolylidene fragments" cited in the application see pages 1331,1332,compound XXVIII ---	1
X	CHEMISTRY OF MATERIALS, vol. 6, no. 7, 1994, WASHINGTON US, pages 1023-1032, XP002028006 ROBERT D.MILLER ET AL: "Substituted azole derivatives as nonlinear optical chromophores" cited in the application see page 1025,compound 10b ---	1
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 2, 19 January 1996, WASHINGTON US, pages 446-457, XP002028007 PAMELA BROWN ET AL: "The chemistry of pseudomonic acid.Synthesis and antibacterial activity of a series of 5-alkyl,5-alkenyl, and 5-heterosubstituted oxazoles" see page 449 compounds 2u and 2v -----	1,18-30

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/03857

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 22, 24, 27-30 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/JP 96/03857

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0087953 A	07-09-83	AU 563067 B	25-06-87
		AU 1185383 A	01-09-83
		CA 1195983 A	29-10-85
		DE 3376424 A	01-06-88
		HK 47091 A	21-06-91
		JP 6004627 B	19-01-94
		JP 58159491 A	21-09-83
		US 5041567 A	20-08-91
		US 4812470 A	14-03-89
WO 9524403 A	14-09-95	AU 1816495 A	25-09-95
		CA 2182520 A	14-09-95
		EP 0749433 A	27-12-96
		FI 963539 A	09-09-96
		NO 963776 A	07-11-96
		PL 316175 A	23-12-96
WO 9513067 A	18-05-95	EP 0727998 A	28-08-96